Neurological Sciences

Supplementary Material 1

Predominant neurological phenotype in a Hungarian family with two novel mutations in the *XPA* gene - case series

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Supplementary Material 1.1

Legend for Supplementary Material 2. The video demonstrating the neurological assessment of patient II-2.

Supplementary Material 1.2

Cognitive characterization of patients with XPA.

	Father	**Mother**	**Patient II-1**	**Patient II-2**	**Patient II-3**	**Patient II-4**	**Patient II-5**
Age at examination (years)	62	60	42	39	36	34	25
Years of education	17	11	10	11	13	12	12
Estimated premorbid IQ							
NART (max. 100%)	87%	81%	82%	-	57%	63%	67%
Degree of overall impairment							
MMSE (max. 30 p)	30	28	24	19	26	27	28
ACE (max. 100 p)	89	84	63.5	35	64	70	87
Severity of impairment	-	+	++	+++	++	++	-
Verbal memory							
ACE anterograde memory (max. 7 p)	5	0	0	0	1	3	7
RBMT story delayed recall (max. 21 p)	5	6.5	0.5	-	3	0	4
Severity of impairment	+	++	+++	+++	++	++	+
Non-verbal memory							
RBMT face recognition delayed recall (max. 10 p)	10	9	10	5	8	8	9

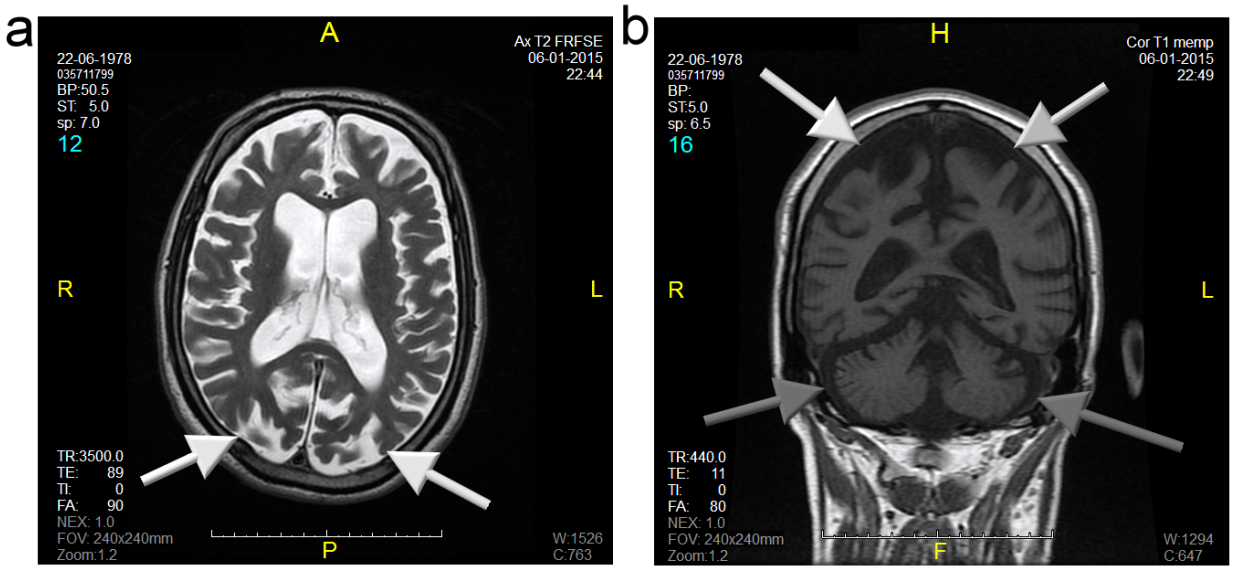
RBMT picture recognition delayed recall (max. 20 p)	20	20	19	8	20	20	20
Severity of impairment	-	-	-	+++	-	-	-
Simple working memory							
DST	8	6	5	-	5	5	6
RBMT story immediate recall (max. 21 p)	11	7.5	2.5	-	4.5	0	6
CBTT	4	4	4	-	4	3	3
Severity of impairment	-	-	+	N.A.	+	+	+
Complex working memory							
LST	3	2.66	1.66	-	1.66	1.66	2
BDST	5	4	4	-	3	3	4
Severity of impairment	-	+	++	N.A.	++	++	+
Language							
ACE language (max. 28 p)	27	28	28	26	22	26	28
Severity of impairment	+	-	-	+	++	+	-
Attention							
Pieron test N (max. 400 p)	200	237	123	180	200	60	130
Pieron test T% (max. 100%)	98	96	84	51	81	78	96
Severity of impairment	-	-	+	+++	+	++	-
Executive functions							
Letter fluency	6.33	11	7.66	-	6.66	8.33	8.66

Semantic fluency	15	19.5	12	-	8.5	7.5	14.5
Episodic fluency	18	19	16	-	9	9	15
Verb fluency	19	16	14	-	4	7	14
TMT Part B (sec)	192	75	520	-	321	690	143
TMT Part B error	3	0	7	-	4	10	1
Severity of impairment	++	-	+++	N.A.	++	+++	++
Visuospatial skills							
BVMT-R (max. 12 p)	12	12	10	6	12	12	12
ACE figure drawing (max. 2 p)	2	2	2	0	2	1	1
Severity of impairment	-	-	+	+++	-	+	+
Processing speed							
TMT Part A (sec)	63	43	116	-	88	105	43
TMT Part A error	0	0	0	-	0	0	0
Severity of impairment	++	+	++	N.A.	+++	+++	+
Mood							
BDI (max. 63 p)	8	7	29	-	8	7	6
Severity of impairment	-	-	+++	N.A.	-	-	-
Anxiety							
STAI-S	32	38	47	-	30	37	41
STAI-T	37	46	49	-	36	45	35
Severity of impairment	-	-	-	N.A.	-	-	-

The demonstrated cognitive dysfunction is caused by the impairment of two functional neuroanatomical networks, the hippocampus-dependent and that related to the prefronto-cerebellar system, with similar degrees of impairment. The mother has an overall slight (ACE: 84 points) cognitive disability which is seemingly attributed to her poor performance in anterograde verbal memory test. This alteration may be the consequence of regular benzodiazepine use. Despite the lack of severe depression or anxiety, the patient takes this medication to keep with the stressful events related to the care of her disabled children. Regarding the father, the impairment in overall cognitive functions is not clinically significant (ACE: 89 points, MMSE: 30 points), but the executive functions and processing speed are seemingly decreased. The reason behind that may be the presence of severe insomnia accompanied with occasional daytime somnolence. Nevertheless, both parents should be controlled for further progression.

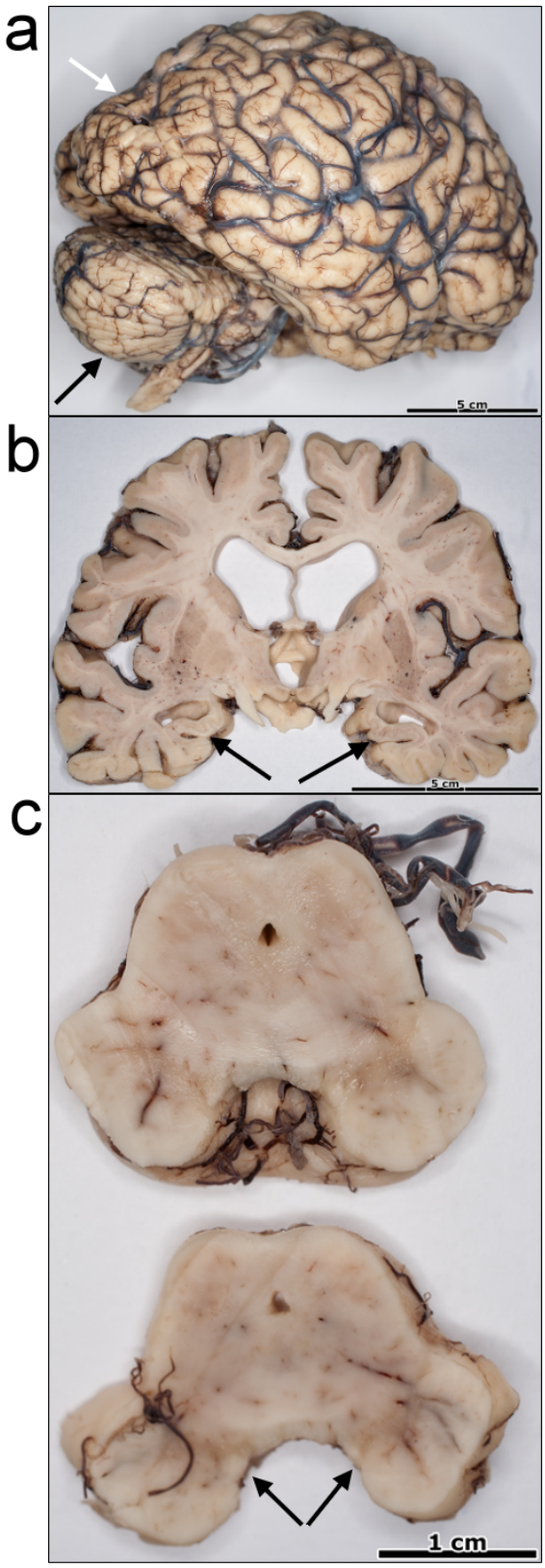
ACE: Addenbrooke's Cognitive Examination, BDI: Beck Depression Inventory, BDST: Backward Digit Span Task, BVMT-R: Brief Visuospatial Memory Test-Revised, CBTT: Corsi Block-Tapping Test, DST: Digit Span Task, LST: Listening Span Task, MMSE: Mini-Mental State Examination, N.A.: not available, NART: National Adult Reading Test, RBMT: Rivermead Behavioural Memory Test, STAI: The State-Trait Anxiety Inventory, TMT: Trail Making Test

Supplementary Material 1.3



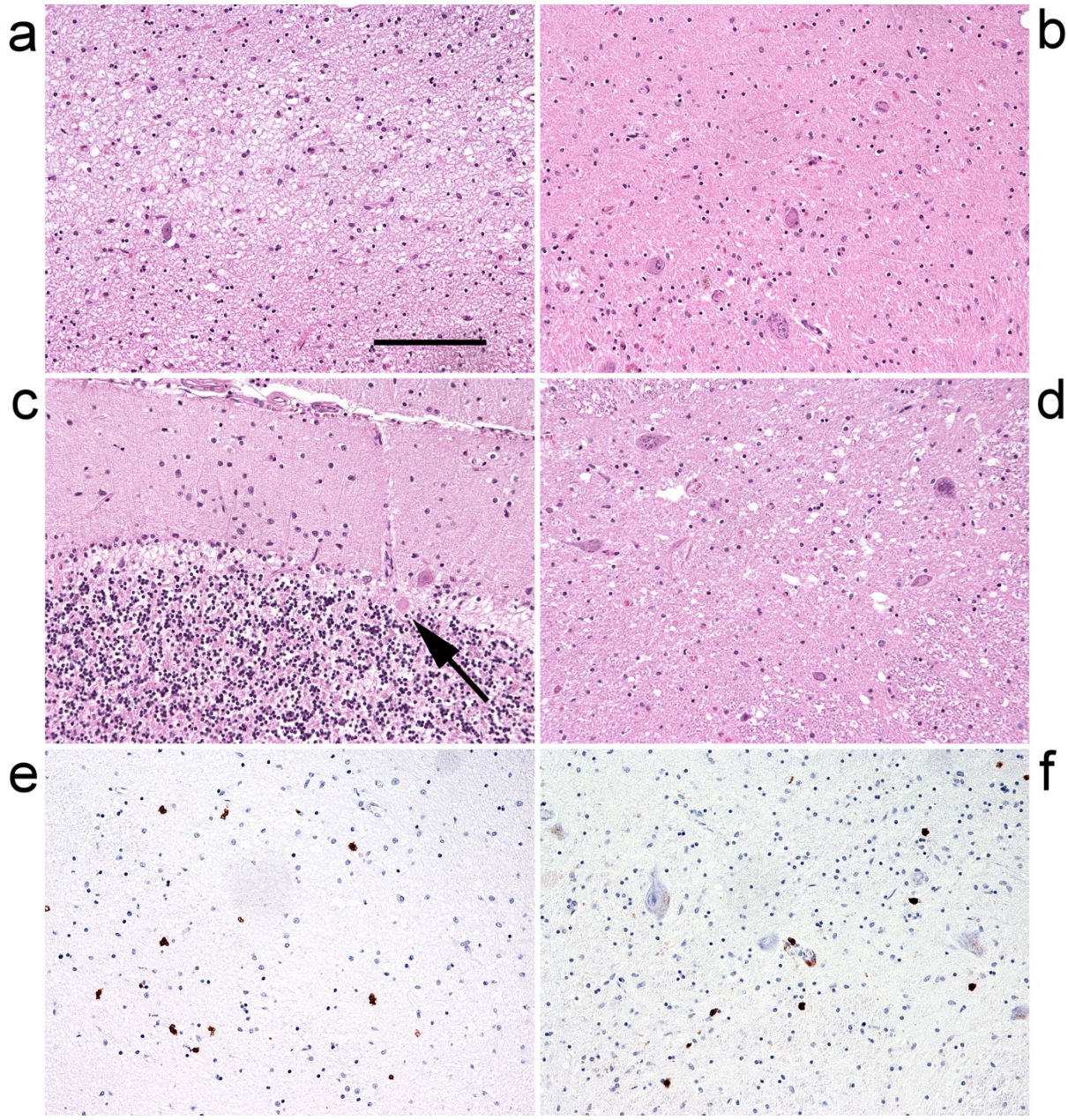
Brain magnetic resonance imaging of the proband with XPA. T2-weighted axial images (1.5 Tesla) **(a)** and T1-weighted coronal images (1.5 Tesla) **(b)** demonstrate generalized brain atrophy with slight predominance at the parieto-occipital region (indicated with white arrows) and in the cerebellum (indicated with gray arrows) in patient II-2.

Supplementary Material 1.4



Macroscopic neuropathological alterations of the proband with XPA. The total brain weight was 815 grams, the cerebellum-brainstem weight was 115 grams. The external examination of the hemispheres, especially that of the parieto-occipital region (**a**; white arrow), and the cerebellum-brainstem (**a**; black arrow) revealed marked atrophy. On the coronal sections a prominent thinning of the cortical ribbon and the cerebellar folia could be seen and the volume of the white matter was also decreased. The hippocampus was markedly atrophic on both sides (**b**; black arrows). The heads of the caudate nuclei were symmetrically flattened. The thalamus and lentiform nuclei showed mild atrophy. A remarkable ventricular dilatation and spacing in the Sylvian fissure could be seen. The cross-sections of the brainstem revealed an almost complete discoloration of the substantia nigra (**c**; black arrows). The anterior and posterior horn of the spinal cord and the spinal nerves were proportionately atrophic. In addition to the marked atrophy behind considerably decreased brain weight, the craniometric measurements may raise the possibility of slight microcephaly in patients II-1 and II-2, but no microcephaly could be demonstrated in other family members.

Supplementary Material 1.5



Microscopic *post mortem* neuropathological alterations of the proband with XPA. Formalin-fixed (*post mortem* delay of 600 hours), paraffin-embedded tissue blocks (2.5 x 2.0 cm) were applied. The presence of astrogliosis/microgliosis/neuronal loss, and degree of various protein depositions were semi-quantitatively (none, mild, moderate, severe) evaluated in the following anatomical regions: frontal, temporal, occipital and premotor cortex, basal ganglia and thalamus, amygdala, hippocampus and brainstem levels (mesencephalon, pons, medulla oblongata). Histological examination revealed mild loss of neurons with edema-related spongy loosening of the neuropil in the superficial layers of cortical areas. There was a lack of ballooned neurons or eosinophilic inclusion bodies. The basal ganglia, thalamus and amygdala were also relatively well preserved. In the hippocampus we observed prominent loss of neurons and reactive astrogliosis in the CA1

(**a**; H&E staining) and CA4 subregions. This was asymmetrical and involved mostly the left side. Further mild to moderate neuronal loss was seen in the substantia nigra (**b**; H&E staining) and severe loss was observed in the cerebellum (**c**; H&E staining, arrow indicates a torpedo), where the Purkinje cell layer showed significant depletion with Bergmann-gliosis and formation of axonal torpedos. Other brainstem nuclei did not show relevant neuronal loss, except for moderate gliosis in the inferior olives. The anterior horn motor neurons were moderately depleted (**d**; H&E staining). There was a lack of vascular lesions in the examined areas. Microglial activation was seen in areas with neuronal loss and additionally scattered CD8 positive cytotoxic T cells, but no CD20 positive B cells, were also observed in the hippocampus (**e**), substantia nigra (**f**), cerebellar white matter and dentate nucleus. In further anatomical regions mild CD8 positive cell infiltrations were seen around vessels in the white matter. Immunostaining for α-synuclein, amyloid-beta, TDP-43, phospho-TDP-43, ubiquitin and p62 did not reveal pathological protein deposits in any of these regions. In the immunostaining for phospho-tau only a single neuron was seen in the entorhinal cortex on the side where sclerosis was observed.
The bar in (**a**) represents 50 micrometer for all images.

Method for immunohistochemistry: In addition to Hematoxylin and Eosin and Luxol Fast Red, the following monoclonal antibodies were used for immunohistochemistry: anti-tau AT8 (pS202/pT205, 1:200, Pierce Biotechnology, Rockford, IL, USA), anti-phospho-TDP-43 (pS409/410, 1:2,000, Cosmo Bio, Tokyo, Japan), anti-α-synuclein (1:2,000, clone 5G4, Roboscreen, Leipzig, Germany), anti-Aβ (1:50, clone 6F/3D, Dako, Glostrup, Denmark), anti-p62 (1:1,000, BD Transduction, Lexington KY, USA), anti-ubiquitin (1:50,000, Millipore, Temecula, CA, USA), TDP-43 (1:2,000, Abnova Corp., Taipei City, Taiwan), anti-CD8 (1:100, DakoCytomation, Glostrup, Denmark), and anti-HLA-DR (clone CR3/43, 1:100, DakoCytomation, Glostrup, Denmark). The DAKO EnVision© detection kit, peroxidase/DAB, rabbit/mouse (Dako, Glostrup, Denmark) was used for visualization of antibody reactions.

Supplementary Material 1.6

Detailed description of the neurological and related alterations of patient II-1 and legend for Supplementary Material 3. Besides the presence of an exaggerated sunburn reaction from her infancy, the symptoms of patient II-1 became manifest at the beginning of her 30s. She presented memory problems, as well as speech and gait disturbances.
Regarding the neurological and neuropsychological examination of patient II-1, the following alterations were observed: disturbed eye movements (exophoria, saccadic eye movements with

restricted gaze in the upward direction), dysarthria, hypo-/areflexia, bilateral palmomental sign, movement disorder with dominating ataxia (bilateral dysmetria, cerebellar predominant mixed limb ataxia more pronounced in the legs, truncal ataxia, severe postural instability, broad-based, ataxic gait, and mild postural tremor), decreased sense of vibration, moderate cognitive dysfunction and severe depression (Supplementary Material 1.2; The video demonstrating the neurological assessment of patient II-1 is uploaded as Supplementary Material 3).
The brain MRI revealed generalized atrophy with slight predominance regarding the parieto-occipital and cerebellar structures.
Audiological screening demonstrated only slight sensorineural hearing impairment at low frequencies.

Supplementary Material 1.7

Detailed description of the neurological and related alterations of patient II-3 and legend for Supplementary Material 4. The neurological symptoms of patient II-3 became manifest at the beginning of his 30s. Upon examination he presented disturbed eye movements (saccadic eye movements with restricted gaze in the upward direction), dysarthria, hypo-/areflexia, slight muscle hypotonia, bilateral palmomental sign, movement disorder with dominating ataxia (mainly left-sided bilateral dysmetria, cerebellar predominant mixed limb ataxia more pronounced in the legs, truncal ataxia, severe postural instability, broad-based, ataxic gait, mild postural tremor, occasional spontaneous distal myoclonic jerks which can be exacerbated by sensory stimuli thereby presumed to be cortical origin) and moderate cognitive dysfunction (Supplementary Material 1.2; The video demonstrating the neurological assessment of patient II-3 is uploaded as Supplementary Material 4). Only a slightly exaggerated sunburn reaction was present.
Audiological screening demonstrated slight hearing impairment at low frequencies on the left side and at high frequencies on the right side.

Supplementary Material 1.8

Detailed description of the neurological and related alterations of patient II-4 and legend for Supplementary Material 5. In addition to the presence of pronounced light sensitivity, complicated scar healing and disturbed vision, the neurological symptoms of patient II-4 became manifest at approximately in the middle of his 20s. Upon examination disturbed eye movements (saccadic eye movements with restricted gaze in the upward direction, gaze-evoked nystagmus), dysarthria, hypo-/areflexia, bilateral palmomental sign, movement disorder with dominating ataxia (bilateral dysmetria, cerebellar predominant mixed limb ataxia more pronounced in the legs, truncal ataxia, severe postural instability, broad-based, ataxic gait, mild postural tremor,

slight left-sided bradykinesia), parietal lobe signs (left-right disorientation, dressing apraxia), decreased sense of vibration and moderate cognitive dysfunction were detected (Supplementary Material 1.2; The video demonstrating the neurological assessment of patient II-4 is uploaded as Supplementary Material 5).

The brain MRI revealed atrophy predominantly affecting the parieto-occipital and cerebellar structures.

Electroneurography demonstrated mixed sensorimotor lower limb predominant polyneuropathy.

Audiological screening did not show any hearing abnormality.

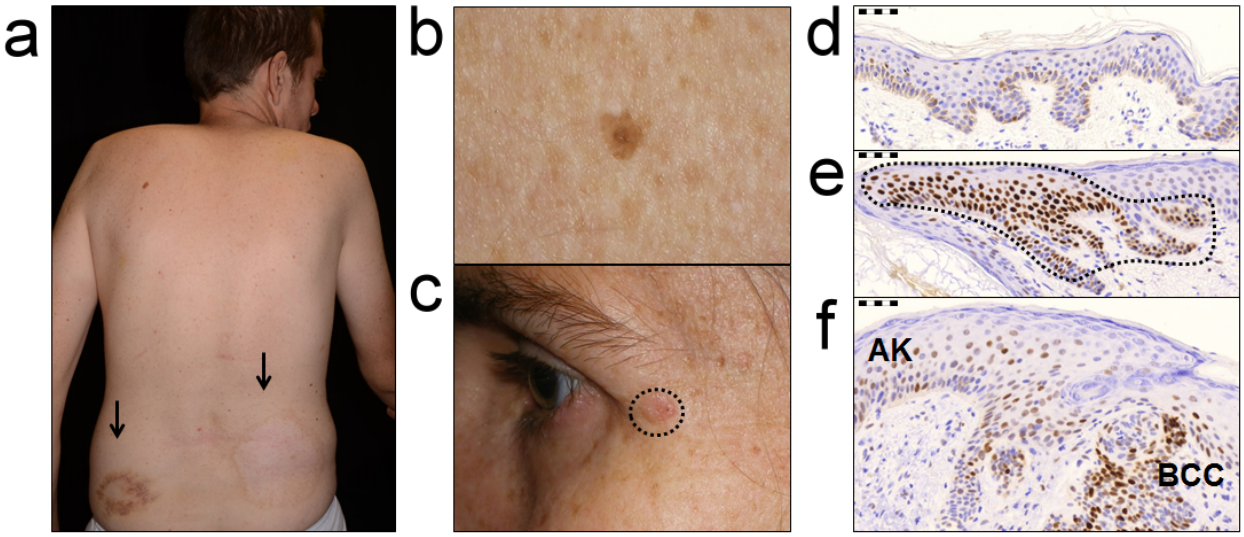
Supplementary Material 1.9

Detailed description of the neurological and related alterations of patient II-5 and legend for Supplementary Material 6. In addition to pronounced light sensitivity and slightly disturbed speech, patient II-5 does not have any major complaint. The neurological examination of patient II-5 identified mainly minor alterations: saccadic eye movements, slight dysarthria, hyporeflexia, palmomental sign on the left side, cerebellar predominant mixed limb ataxia more pronounced in the legs, slightly broad-based, ataxic gait, and only mild-to-moderate cognitive impairment (Supplementary Material 1.2; The video demonstrating the neurological assessment of patient II-5 is uploaded as Supplementary Material 6).

The brain MRI demonstrated only slight atrophy mainly affecting the parieto-occipital region and the cerebellum.

Audiological screening did not show any hearing abnormality.

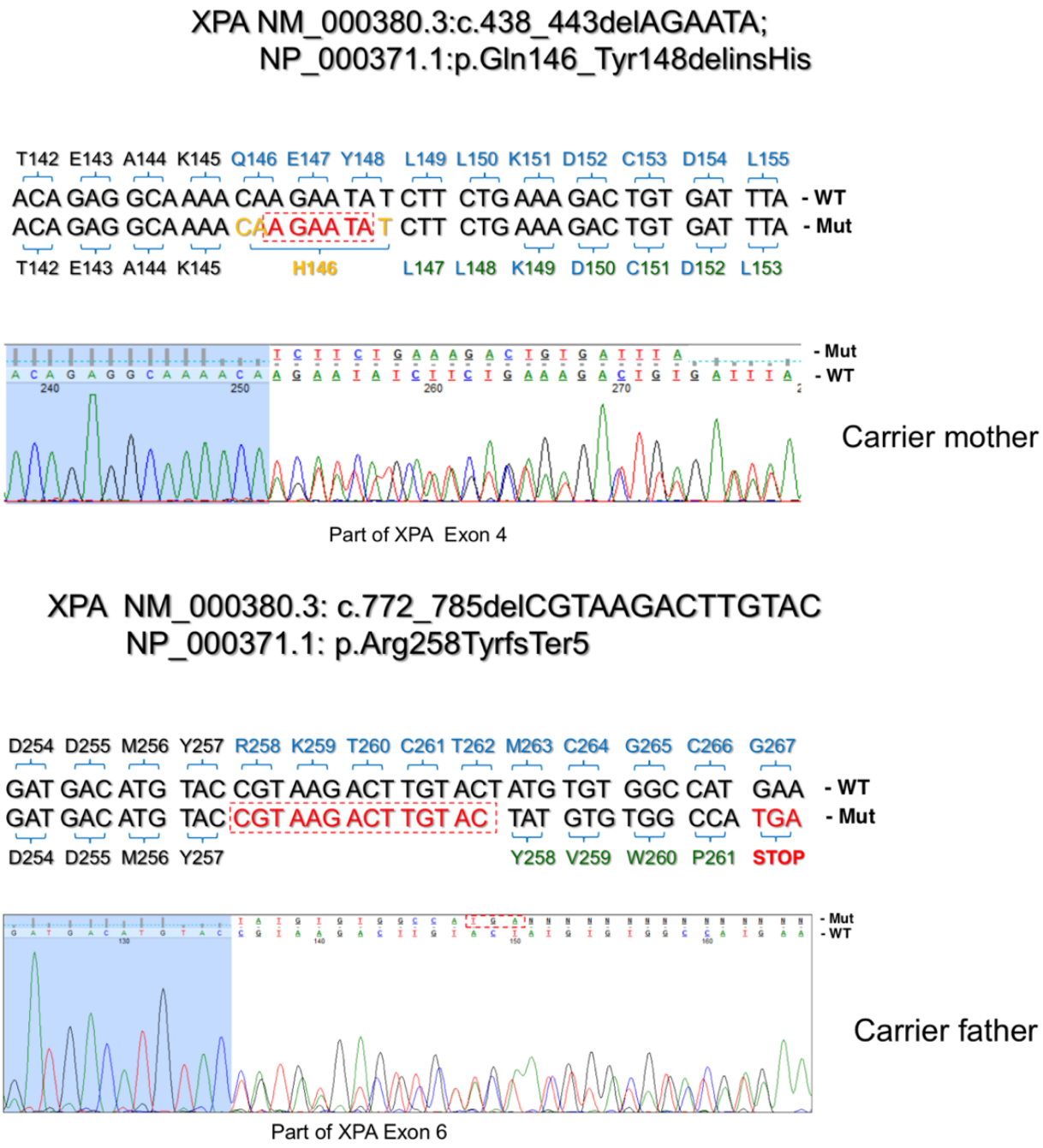
Supplementary Material 1.10



Representative clinical and histopathological pictures of dermatological alterations of the XPA family members. Among the family members, solar lentigos and lentiginous naevi were more numerous in patients II-1 and II-2, and scattered foci of basal cell carcinoma appeared and were excised from the nasal and periorbital areas. Patient II-2 exhibited solar lentigos on the upper back and shoulder areas, note the foci of healing suffusions resulting from previous traumatisation (**a** - arrows). Patient II-1 has multiple solar lentigos affecting diffuse facial, as well as trunk and arm regions; dotted line marks a focus of nodular basal cell carcinoma (**b**, **c**). Histopathologically, solar affected back skin shows basal hyperpigmentation in the keratinocytes with some elongation of the rete ridges (**d**), and with foci of p53 mutated clones (**e** – dot mark). In addition of actinic keratosis (AK), basal cell carcinoma (BCC) nests from facials tumours have p53 protein accumulation as well (**f**, IHC, brown colorimetric reaction; OM 112x). In the younger brothers, only lentigos were noted on the sun-exposed skin. Written informed consent was obtained from the participants of the study for the publication of photo materials with identifying information. The bars in (**a**), (**b**) and (**c**) represent 50 micrometer.

Method for immunohistochemistry: Following punch biopsy of the sun-exposed skin, p53 immunohistochemistry (clone PA0057 ready to use dilution with heat induced epitope retrieval at pH = 9 for 30 minutes; Leica Biosystems, UK) was performed.

Supplementary Material 1.11

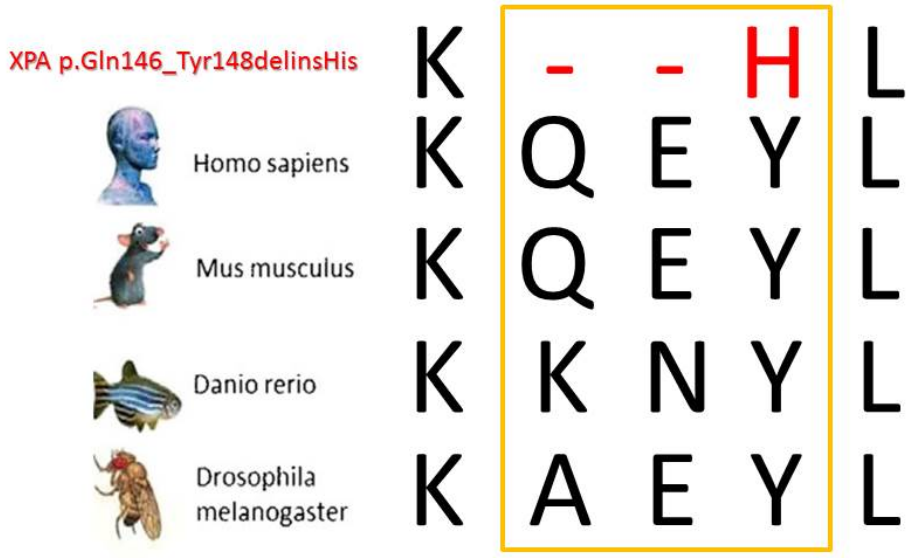


Sanger sequencing of the identified XPA mutations in the carrier parents and the detailed description of genomic studies. In light of dominating cerebellar and cognitive dysfunction and the pseudo-dominant pattern of inheritance the main causes of dominantly inherited ataxia (*ATXN1*, *ATXN2*, *ATXN3* and *TBP* genes) and cognitive dysfunction (*FMR1*, *PSEN1*, *PSEN2* and *APP* genes) were assessed first, finding no relevant alteration. Therefore, targeted gene analysis by clinical exome sequencing was performed to find the pathogenic alteration behind the severe clinical phenotype. After obtaining written, informed consent, genomic DNA was extracted from peripheral blood leukocytes by standard protocol. For clinical exome sequencing, a total of 60 ng

of genomic DNA was used for library preparation and sequenced with TruSight One clinical exome kit (Illumina) on Illumina MiSeq platform. The clinical exome kit covers the coding region of 4813 clinically relevant, disease-associated genes. The 150-bp paired reads were aligned to the GRCh37.75 human reference genome by Burrows Wheel Aligner (BWA v0.7.9a) software. The variants were called by Genome Analysis Toolkit Haplotype Caller (GATK v3.5) best practice and annotated by SnpEff and VariantStudio softwares.

Parents of the index patient were tested for phase establishment. We could confirm that the 2 pathogenic variants identified in the index patient were in trans phase since the mother was heterozygous for the variant in exon 4, whereas the father was heterozygous for the variant in exon 6 of the XPA gene. The likely pathogenic feature of the in-frame mutation in exon 4 (p.Gln146_Tyr148delinsHis) is supported by that it affects a conserved region of the protein (presented in Supplementary Material 1.12) including p.Glu147 and p.Tyr148, the deletion of which results in the pathologically reduced binding of XPA to replication protein A. The second one in exon 6 (p.Arg258TyrfsTer5) maybe considered pathogenic as it eventuates a premature stop codon. The alterations found by clinical exome sequencing were also confirmed by Sanger sequencing in cases of all available family members (the variants of carrier parents are presented above).

Supplementary Material 1.12



The figure demonstrates that the in-frame mutation is located in a conserved region of the XPA protein.

Supplementary Material 1.13

The demographic and clinical characteristics of patients with mutations in the *XPA* gene.

Mutation (DNA)	Mutation (Protein)	Exon/ Intron	Case number	Nation	Gender (M/F)	Age of onset (years)	Skin symptoms	Cancer	Mental retardation	Cerebellar symptoms	Pyramidal signs	Hearing impairment	Ocular signs	References
c.172+2T>G + c.390-1G>C	Int. 1 + Int. 3	Int. 1 Int. 3	1	Japanese	1/0	<1	+++	-	-	-	-	NA	NA	1
c.253C>T	p.Gln85Ter	2	1	Bangladeshi	0/1	5[#]	++	-	++	++	++	NA	+	2
c.266_267dupAA	p.Val90fs	2	1	United Kingdom	1/0	<1	++	-	++	++	++	NA	+	2
c.268_269insAA	p.Val90KLysfs*14	2	1	Moroccan	1/0	<1	+++	P	+++	NA	NA	NA	NA	3
c.283G>A	p.Gly95Arg	2	1	Finnish	ND	<1	+++	P	P	P	-	-	+	4
c.283G>A + c.631C>T	p.Gly95Arg + p.Arg211Ter	2, 5	1	Chinese	1/0	<1	P	-	P	P	-	P	P	5
c.314G>A	p.Cys105Tyr	3	2	Somali	1/1	8, 12[#]	+/++	-	++	++	++	NA	+	2
c.323G>T + c.349_353delCTTAT	p.Cys108Phe + p.Lys117Glufs*4	3	1	Caucasian	NA	NA	NA	NA	NA	NA	NA	NA	NA	6
c.331G>T	p.Glu111Ter	3	4	3 Tunisian, 1 Egyptian	3/1	<1	+++	P	+++	-: 1 ++: 2 +++: 1	P	NA	P: 2	7, 8
c.331G>T + c.389+1G>C	p.Glu111Ter + Int. 3	3, Int. 3	1	Chinese	1/0	<1	P	-	P	P	-	P	P	5
c.335_338delTTATinsCATAAGAAA	p.Phe112Serfs*2	3	2	Indian	0/2	<1	P	-	P	P	P	P: 1 -: 1	P	9
c.348T>A	p.Tyr116Ter	3	1	Japanese	0/1	<1	+++	P	+++	P	P	NA	NA	10
c.348T>A + c.390-1G>C	p.Tyr116Ter + Int. 3	3, Int. 3	4	Japanese	M: 2 NA: 2	early childhood	+: 1 +++: 2 P: 1	-: 1 P: 1 NA: 2	-: 1 +++: 3	-: 1 ++: 1 +++: 2	-: 1 +++: 2 NA: 1	P: 1 NA: 3	+: 1 NA: 3	11, 12, 13

c.349_353delCTTAT	p.Leu117Glufs*4	3	3	2 Indian, 1 Iranian	1/2	<1	++: 1 P: 2	-: 2 NA: 1	P	P: 2 NA: 1	-: 2 NA: 1	-	++: 1 P: 2	9, 14
c.374delC	p.Pro125Ilefs*15	3	2	1 Caucasian, 1 Egyptian	F: 1 NA: 1	<1, NA	+: 1 NA: 1	-: 1 NA: 1	+: 1 NA: 1	-: 1 NA: 1	-: 1 NA: 1	NA	+: 1 NA: 1	6, 8
c.378T>G	p.Cys126Trp	3	1	Indian	1/0	<1	P	-	P	P	P	-	P	9
c.389G>A	p.Arg130Lys	3	2	Black (breed)	NA	NA	++: 1 NA: 1	-: 1 NA: 1	NA	NA	NA	NA	P: 1 NA: 1	15
c.389+1G>T + c.631C>T	Int. 3 + p.Arg211Ter	5, Int. 3	1	Chinese	1/0	<1	P	P	P	P	-	P	-	5
c.390-1G>C	Int. 3	Int. 3	60	57 Japanese, 3 Chinese	28/16 NA: 16	<1: 42 3: 1 NA: 17	++: 18 +++: 15 P: 10 NA: 17	P: 15 -: 23 NA: 22	+: 4 ++: 10 +++: 11 -: 12 P: 3 NA: 20	+: 4 ++: 12 +++: 7 -: 12 P: 3 NA: 22	+: 4 ++: 6 +++: 6 -: 13 NA: 31	P: 23 -: 15 NA: 22	+: 1 ++: 15 +++: 10 P: 2 NA: 32	5, 11, 12, 13, 16, 17, 18, 19, 20, 21, 22
c.390-1G>T + c.555G>C	Int. 3 + p.Gln185His	4, Int. 3	1	Caucasian	NA	NA	NA	NA	NA	NA	NA	NA	NA	23
c.390-1G>C + c.619C>T	Int. 3 + p.Arg207Ter	5, Int. 3	1	Japanese	1/0	<1	+	-	+	+	+	-	+	11
c.390-1G>C + c.622C>T	Int. 3 + p.Gln208Ter	5, Int. 3	1	Japanese	1/0	<1	+++	-	+++	+++	-	P	P	24
c.390-1G>C + c.682C>T	Int. 3 + p.Arg228Ter	6, Int. 3	12	Japanese	2/7 NA: 3	<1: 8 4:1 NA: 3	+: 6 ++: 4 P: 2	P: 4 -: 8	+: 6 ++: 2 +++: 3 -: 1	+: 6 ++:2 -: 4	+: 6 -: 1 NA: 5	P: 4 -: 4 NA: 4	+: 2 NA: 10	11, 12, 13, 17, 25, 26, 27
c.390-1G>C + c.690insT	Int. 3 + p.231Lysfs*15	6, Int. 3	1	Japanese	1/0	NA	+	-	+	+	-	NA	NA	28
c.390-1C>T + c.779insTT + c.780insTT	Int. 3 + p.Thr260Ilefs*8	6, Int. 3	3	Japanese	1/2	NA	+	-	+	+	-	NA	NA	28
c.390-1G>C + ?	Int. 3 + ?	Int. 3 + ?	3	Japanese	1/2	<1	P	P: 1 -: 2	++: 1 +++: 1 -: 1	++: 2 +++: 1	NA	+	NA	13

c.428_429delAG	p.Glu143Glyfs*11	4	2	Indian	NA	<1	P	-	P	P	P: 1 -: 1	P	P	9
c.438_443delAGAATA + c.772_785delCGTAAGACTTGTAC	**p.Gln146_Tyr148del_insHis + p.Arg258Tyrfs*5**	**4, 6**	**5**	**Hungarian**	**4/1**	**13-14: 1** **~25: 2** **~30: 2**	**+: 3** **++: 2**	**P: 2** **-: 3**	**++: 3** **+++: 1** **-: 1**	**+++: 4** **+: 1**	**+: 1** **-: 4**	**+: 2** **-: 2** **NA: 1**	**-: 5**	
c.451A>T	p.Lys151Ter	4	1	Chinese	0/1	<1	+	-	P	NA	NA	-	-	29
c.467_486del20nt + c.665insA	p.Lys157Ilefs*13 + p.Val223Serfs*22	4, 5	2	NA	0/2	+	NA	-	-	-	-	-	-	30
c.482delC + c.538_539delCT	p.Pro161fs*6 + p.Tyr181Leufs*11	4	1	Chinese	1/0	1.5	P	-	P	P	-	P	P	5
c.529G>A	p.Asp177Asn	4	1	Japanese	0/1	62[#]	++	P	-	-	-	-	-	31
c.553C>T	p.Gln185Ter	4	2	Egyptian	0/2	<1	+++	P: 1 -: 1	-	-	P: 1 -:1	NA	++: 1 +++: 1	8
c.555G>C	p.Gln185His	4	1	Caucasian	NA	NA	+	NA	+	+	+	P	NA	15
c.555G>C + c.631C>T	p.Gln185His + p.Arg211Ter	4, 5	1	Caucasian	NA	NA	NA	NA	NA	NA	NA	NA	NA	15
c.555G>C + c.731A>G	p.Arg185His + p.His244Arg	4, 6	1	Caucasian	NA	NA	+	NA	+	+	+	P	NA	15
c.555+8A>G	Int. 4	Int. 4	13	9 Pakistani, 3 Indian, 1 Afghan	7/6	3: 1 4-46[#]: 12	+: 9 ++: 2 -: 2	P: 3 -: 10	-	-	-	-	P: 1 -: 12	2, 32
c.609-2A>G	?[##]	?[##]	1	Northern Africa	NA	NA	NA	NA	NA	NA	NA	NA	NA	33

c.619C>T	p.Arg207Ter	5	4	1 Tunisian, 2 Brazilian, 1 Palestinian	1/2 NA: 1	<1: 3 NA: 1	+++	P: 2 -: 2	+: 2 +++: 2	+++	+++: 1 P: 1 -: 2	P: 1 NA: 3	+: 1 NA: 3	7, 12, 34, 35
c.619C>T + c.622C>T	p.Arg207Ter + p.Gln208Ter	5	2	Chinese	2/0	<1	+++	-	P	NA	NA	-	-	29
c.631C>T	p.Arg211Ter	5	3	Chinese	1/2	<1	+++: 1 P:2	P: 1 -: 2	P	P	-:2 NA: 1	P: 2 -: 1	P:2 NA: 1	5, 36
c.631C>T + c.682C>T	p.Arg211Ter + p.Arg228Ter	5, 6	1	Chinese	1/0	<1	P	-	P	P	-	P	P	5
c.640dupA	p.Met214fs	5	1	Bangladeshi	0/1	1[#]	+	-	++	++	++	NA	+	2
c.647_648delAG	p.Lys217Glufs*3	5	2	Chinese	2/0	<1	+: 1 +++: 1	P: 1 -: 1	P: 1 -: 1	P: 1 -: 1	P: 1 -: 1	P: 1 -: 1	P: 1 -: 1	18
c.654delA	p.Lys218Asnfs*5	5	5	Pakistani	4/1	<1	+++: 3 NA: 2	P: 2 -: 1 NA: 2	-: 3 NA: 2	-: 3 NA: 2	-: 3 NA: 2	-: 3 NA: 2	-: 3 NA: 2	37
c.682C>T	p.Arg228Ter	6	46	17 Tunisian, 10 Moroccan, 7 Northern Africa, 6 Finnish, 2 Pakistani, 2 Japanese, 2 Algerian	18/8 NA: 20	<1: 20 <3: 6 NA: 20	+: 15 ++: 11 +++: 8 -: 3 P: 2 NA: 7	P: 17 -: 22 NA: 7	+: 5 ++: 1 +++: 2 -: 6 P: 17 NA: 15	+: 1 ++: 1 +++: 1 -: 14 P: 10 NA: 19	+: 1 ++: 1 +++: 1 -: 14 P: 10 NA: 19	P:11 -: 11 NA: 24	+: 4 ++: 3 -: 4 P: 10 NA: 25	2, 3, 4, 12, 17, 33, 38, 39, 40, 41, 42
c.682C>T + c.722insG	p.Arg228Ter + p.Val241Glyfs*4	6	3	Tunisian	1/2	25[#], 47, 56	-	-	+	P: 2 -: 1	P: 2 -: 1	P: 1 -: 1 NA: 1	NA: 3	42
c.682C>T + ?	p.Arg228Ter + ?	6	2	Japanese	0/2	<1	P	-	++: 1 -: 1	++	NA	-	NA	13

#: Age at diagnosis.

##: Intronic mutation was proposed, but the given mutation site is exonic (Exon 5).

?: Unknown mutation.

+: mild; ++: moderate; +++: severe; -: absent; NA: not available; P: present, but not detailed, Int: Intron.

Methods

PubMed (MEDLINE) was used as search engine for articles. The key terms for searching were: xeroderma AND pigmentosum AND group A. A total of 3056 articles were screened for mutational spectrum of the *XPA* gene. Out of these papers, 42 contained relevant phenotypic information in connection to the reported genetic alterations. Accordingly, in addition to genetic data, the number of relevant cases, their nationality, gender, the age of onset, the severity of dermatological, ophthalmological, auditory and neurological symptoms and the presence or absence of skin malignancy are reported here.

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