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X-linked adrenoleukodystrophy phenotype is independent of ABCD2 genotype

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ABSTRACT

Strikingly variable clinical phenotypes can be found in X-linked adrenoleukodystrophy (X-ALD) even with the same *ABCD1* mutation. *ABCD2* is the closest homolog to *ABCD1*. Since *ABCD2* overexpression complements the loss of *ABCD1 in vivo* and *in vitro*, we have investigated the possible role of the *ABCD2* gene locus as determinant of X-ALD phenotypes. Sequence and segregation analysis of the *ABCD2* gene, in a large X-ALD family with different phenotypes disclosed that the identical *ABCD2* alleles were inherited in brothers affected by mild (noncerebral) versus severe (childhood cerebral) X-ALD phenotypes. Moreover, two independent association studies of *ABCD2* polymorphisms and clinical phenotypes showed an even allele distribution in different X-ALD phenotypes and controls. Based on these findings *ABCD2* can be excluded as a major modifier locus for clinical diversity in X-ALD. These findings are of particular importance for the attempt of pharmacological induction of *ABCD2* as a possible therapeutic approach in X-ALD.

X-linked adrenoleukodystrophy (X-ALD; MIM #300100) is a neurodegenerative metabolic disease characterized by the elevation of saturated, unbranched very long chain fatty acids (VLCFAs; $\geqslant$C22:0) in tissue and plasma likely due to a combination of increased elongation and impaired β-oxidation of VLCFA [1,2]. A wide spectrum of clinical phenotypes ranging from very mild late onset adrenomyeloneuropathy to childhood rapidly progressive demyelinating disease can be observed even within a single family. It has been speculated that in addition to the obligate defect of the *ABCD1* gene (coding for the adrenoleukodystrophy protein ALDP) both, environmental factors and genetic modifiers, may contribute to this phenomenon [3,4]. *ABCD2* (coding for the adrenoleukodystrophy-related protein; ALDRP) is the closest homologue of *ABCD1* [5,6]. The genomic structure of human [7] and mouse [8] *ABCD2* revealed a striking similarity to *ABCD1*, suggesting a recent duplication event of a common ancestor. The gene products ALDP and ALDRP belong to the family of peroxisomal ATP-binding cassette (ABC) half-transporters. Homo- as well as heterodimerization has been reported to occur between ALDP and ALDRP [9]. The expression pattern of mouse and human *ABCD2* was found to be distinct from that of *ABCD1* [5]. Cell lines or tissues expressing high levels of *ABCD1* expressed no or low levels of *ABCD2* and vice versa [10–12]. This finding was interpreted as an indication that ALDP and ALDRP are not obligatory partners but might rather fulfill similar metabolic functions in different tissues. It was indeed shown, that the impaired VLCFA β-oxidation in ALDP-defective fibroblasts could be corrected by expression of transfected *ABCD2* [13]. Moreover, transgenic overexpression of *Abcd2* in *Abcd1*-deficient mice prevents both VLCFAs accumulation and the neurodegenerative features, whereas double mutants for ABCD1 and ABCD2 exhibit an earlier onset and more severe disease when compared with Abcd1 single mutants [14]. These results provide direct evidence

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for functional redundancy or overlap between both transporters *in vivo* and *in vitro*. These observations have substantiated the concept of a new therapeutic strategy in X-ALD through drug-induced transcriptional upregulation of the "surrogate" gene *ABCD2* [15]. Furthermore, due to the functional similarity of ALDP and ALDRP, *ABCD2* appeared to be a good candidate for being a modifier gene in X-ALD, which may account for the heterogeneity of clinical phenotypes. To test this hypothesis, we performed sequencing and segregation analyses of *ABCD2* within a large X-ALD family, affected by different X-ALD phenotypes but carrying the identical mutated *ABCD1* allele (P484R) [16]. Additionally we have used an *ABCD2* polymorphisms for association studies of mild versus severe X-ALD phenotypes.

Patients, material and methods

Patients. The pedigree of the family is shown in Fig. 1. In all hemizygote brothers and the female carrier, the same (P484R) and no other mutation has been identified in the *ABCD1* gene [16]. Two boys (II-4 and II-7), who suffered from childhood cerebral X-ALD, died at the age of thirteen and nine years, respectively. Three male patients (II-1, adrenomyeloneuropathy; II-3, adolescent onset cerebral X-ALD; and II-9, Addison only at the age of 20) and the female carrier (I-2) showed increased VLCFA levels in fibroblasts, plasma, and leukocytes as compared with controls. Normal values were detected in all other female (II-2) and male (I-1, II-5, II-6 and II-10) members of the family [16]. Clinical, neuropathological, ultrastructural, and neurochemical findings in this family had been described previously [17,18].

Two independent association studies (rs11172566 and rs1172661) were performed enrolling 45 unrelated X-ALD patients (17 childhood cerebral X-ALD; 28 noncerebral X-ALD at any age) and 147 controls in the first study and 72 X-ALD patients and 200 controls in the second. In the latter study, the analysis was focused on two extreme phenotypes: childhood cerebral X-ALD with an onset before the age of 12 ($n = 44$) and "pure" AMN ($n = 28$) where MRI has been performed after the age of 45 years proving the absence of inflammatory demyelination.

Sequence analysis of the coding and promoter region of the human ABCD2 gene. Analyses of patients were performed from genomic DNA isolated from fibroblasts, blood leukocytes, or skeletal muscle. Single exons of the *ABCD2* gene or fragments of the putative promoter region (2903 bp) were PCR-amplified with Taq DNA polymerase (Roche). The PCR products were column-purified using a Qiaquick PCR Purification Kit (Qiagen). Cycle sequencing was performed with a rhodamine didesoxy dye terminator kit (ABI/Perkin-Elmer) using amplification primers and internal primers as given in Table 1. Samples were then separated on an ABI 377 sequencer.

Segregation analysis. Genomic DNA was amplified with marker-specific primers (Table 2) using Taq DNA polymerase (Roche). The fragments were labeled with rhodamine[R110] 2′-deoxycytidine 5′-triphosphate (ABI/Perkin-Elmer), which was added at a final concentration of 1 μM to the PCR-reaction. Fragment-lengths were determined with the GeneScan 672 Software using a GeneScan-350 [ROX] standard (ABI/Perkin-Elmer).

Association studies of ABCD2 and clinical forms of X-ALD. The SNP rs11172566 is located in the 3′-untranslated region of the *ABCD2* mRNA at position 3165 (Ref. sequence NM005164). The A to G polymorphism creates an *Hinf*I restriction site. Using PCR primers Oli283 and Oli284, an 880 bp fragment of the 3′-untranslated region of *ABCD2* (Table 1) is amplified. Genomic DNA was used as template, and PCR fragments were subsequently digested with *Hinf*I (Roche) restriction endonuclease leading to 5 fragments of 32, 37, 60, 317, and 434 bp in case of c.2614A, and to 4 fragments of 32, 37, 60, and 751 bp in case of c. 3165G, respectively, (Fig. 2).

In a separate set of patients the SNP rs11172661, a A to G transition, located in the intron 9 of the *ABCD2* gene (position 2110440 of the Ref. contic sequence NT029419) has been investigated using allele specific sense primers Oli1125 (specific for A) or Oli1126 (specific for G), and antisense primer Oli1127. A 193 bp fragment was amplified in separate reactions. Each set of allele-specific primers was mixed with a pair of primers Oli11 and Oli12 amplifying a 774-bp fragment from the *ASA* gene (Arylsulfatase A) as a PCR control (Fig. 3).

Results

Comparative analyses of ABCD2 DNA sequence in brothers affected by different X-ALD phenotypes

To elucidate the hypothesized role of *ABCD2* in X-ALD, we took advantage of a large X-ALD kindred: Five affected brothers

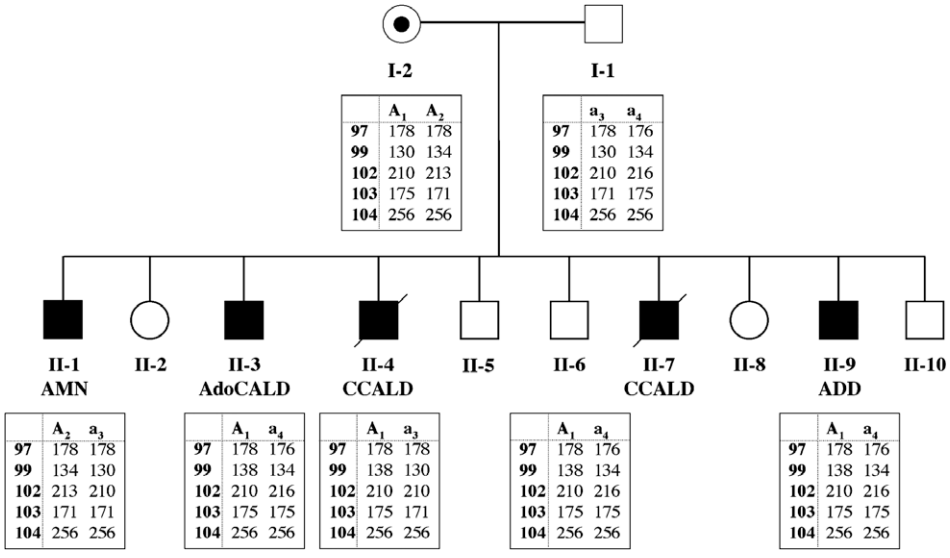

Fig. 1. Pedigree of a large X-ALD family and segregation analysis of the *ABCD2* gene. In all affected brothers and the female carrier, the same mutation (P484R) and no other mutation has been identified in the *ABCD1* gene. Two brothers with CCALD died at the age of thirteen and nine years, respectively (diagonal slash). The markers close to the *ABCD2* gene are listened in Table 3. A1, A2: maternal alleles; a3, a4: paternal alleles. AMN: adrenomyeloneuropathy; AdoCALD: adolescent onset cerebral ALD; CCALD: childhood cerebral ALD; ADD addison only.

Table 1
ABCD2 PCR and sequencing primers

	Forward primer		Reverse primer		Product Size (bp)
	Name	Sequence (5′ → 3′)	Name	Sequence (5′ → 3′)	
Exon 1	Ia	AGACTATGGGACGCTGTAGGAC	Ib	TCTGGCACTGCAGTGGCAACTTG	1111
Exon 2	IIa	AGATGCATAGATAATGCCATAC	IIb	CATAAAACTAGCAATGACAACTTC	346
Exon 3	IIIa	AAAACTCAAGTTTTGTAATTTGTTT	IIIb	ACTAAGTATACTTGGTAATTGAC	234
Exon 4	IVa	AGTCAAGAAGCTTATCTGATTAC	IVb	TGTAACTACTAAAAGCTACCTTC	345
Exon 5	Va	TTAATCAGAATCCTGTGATAATG	Vb	GTATTAGTGTGATGGCAACAATC	196
Exon 6	VIa2	TGCCCAACCTAGGTTATCATG	VIb2	AAGTGGTATTGTCCTACAGAG	456
Exon 7	VIIa	CACACTGAGTAAGTTATCATGAC	VIIb	AAACCACAGACTAAATATATACC	286
Exon 8	VIIIa	TTGTCTAGGGTAGAAATAGTAAC	VIIIb	TTTGGTTACAACAATGGCCTAG	204
Exon 9	IXa	TGTTAGCAATGCAACTCATATTG	IXb	GTGCAACTTAAGAGAAATATGGG	345
Exon 10	Xa	GGGTATCAATTTGAATGATAAACC	37r	CTTAGCTTAACATACTTCATGC	391
Promotor					
PCR1	Prom C2	TTCTGTGTACCATGTTCTGC	Prom3r	GCTGTAGAGATAATCTACTGG	1593
	Prom I[a]	GCAAACAAATGAAGAGATATG			
	Prom Bf[a]	ATTCTTGTTTTGAAGTATTTTC			
	Prom III[b]	CCACGCCCAGCCAAGAGC			
PCR2	Prom Af n	GAATTGTCCTTGACTGTTGAAC	5′RACE2	TCCTAAACAGGAGTTCAGAGAG	1118
	Prom IV[a]	CTATTAGGTTCTGAGACC			
PCR3	5′UT 6f	CATTTTATGTTGATCCTCTTGTCC	#9	CTTGCCAATGATGGGATAGAGG	888
Polymorphism					
rs11172566	Oli283	GCTTTGAACAATTGGATACTG	Oli284	TTTCTGTATTGGCAATTCTC	880
rs11172661	Oli1125	CACTTAATCCTTTGGGGCAA	Oli1127	AAAGACATGGAAAAATCCAGTGA	193
	Oli1126	CACTTAATCCTTTGGGGCAG			
ASA-control	Oli11	ATGACCTCATGGCCGACGCCCAGCGCCAGG	Oli12	AGGGTTCCAAGGAGAGGGCCTGCGGACTGA	774

[a] Internal forward sequencing primer.
[b] Internal reverse sequencing primer.

Table 2
Markers close to the *ABCD2* gene

No.	Marker	Alias	Forward primer (5′ → 3′)	Reverse primer (5′ → 3′)	Repeat type
97	D12S331	AFM092wd11	TAACATTTATTCATCTCCATACTGA	ACATGTAAGAGAGNAAGTTTACAAA	CA
99	D12S1029	CHLC.GATA47G02	ATACCTCCTTTTGGAAGAGTAGA	ATTTTACAAAGGAAAACCTGTTG	Tetranucleotide
102	D12S1048	CHLC.ATA29H01	GGTCTGCTTAGGTCCCTTTT	AAGGAACCAAGGAGTGGAAG	Trinucleotide
103		AFMA106VD5	CAAATGTATCTGGTAAGCCCTAGAG	TTAATTCCTTTGATGATATTCACCG	CA
104	D12S315	AFM210WF6	AATAATGTCTCTCACGGTGC	TGTAGTAATGTCTATAATGTGCCTG	CA

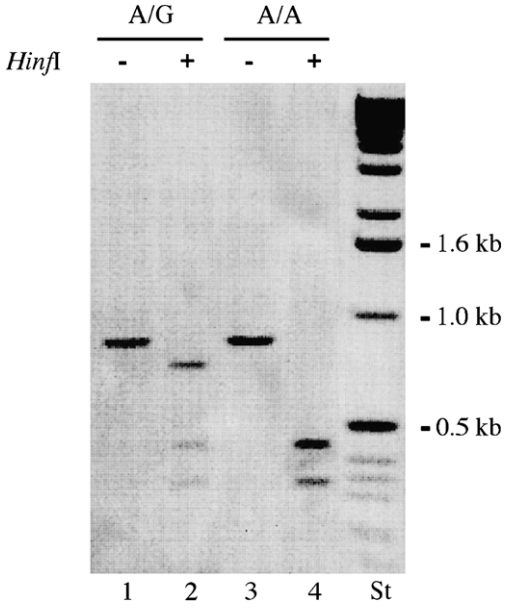

Fig. 2. Restriction endonuclease assay of polymorphism rs11172566 (A → G) within the 3′-UTR of the *ABCD2* gene. 1, 3: undigested PCR product (880 bp); 2,4: HinfI digestion; The A-allele leads to products of 32, 37, 60, 434 and 317 bp; The G-allele leads to products of 32, 37, 60 and 751 bp; 2: Heterozygosity for A/G; 4: Homozygosity for the A allele. St, nucleic acid standard.

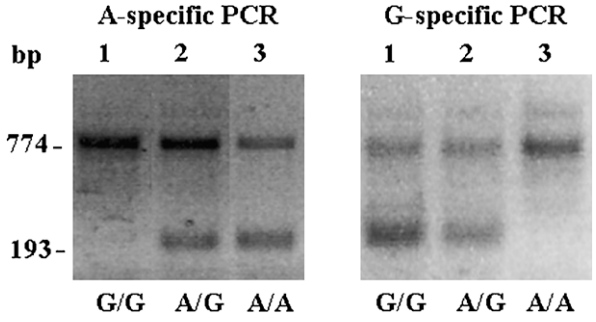

Fig. 3. Allele specific PCR assay of polymorphism rs11172661 in intron 9. Separate PCR reactions are performed using A (left side) or G (right side) specific primers respectively. The geneotipe of the numbers 1–3 represent three patients with the genotype indicated at the bottom of the gel. The size of the 774 bp ASA control fragment and the 193 bp ABCD2 allelspecific fragment are indicated at the right margin.

presenting with four different X-ALD phenotypes, ranging from severe cerebral demyeliniation (II-3, II-4, II-7) to mild noncerebral forms (II-1, II-9) of X-ALD (Fig. 1). To study the influence of the *ABCD2* gene on the phenotypic variability within this family, we performed *ABCD2*-mutation analysis. By sequencing all coding exons and exon-flanking regions of patients II-1, II-3, II-4, and II-9, we could not reveal any difference to the wild type sequence of *ABCD2*. In addition to the coding regions and the exon-intron

boundaries of the *ABCD2* gene, we sequenced a 2903 bp region upstream the translational start codon representing the putative promoter region in a severe cerebral phenotype (II-4) and a noncerebral mild phenotype (II-9). This region includes a 1.3 kb segment that has been reported to exhibit functional promotor activity and which is sufficient to stimulate transcription of a reporter gene by 9-cis-retinoic acid and forskolin [19]. Moreover, a functional regulatory element has been identified within this region consisting of a sterol regulatory element (SRE), which overlaps with a direct repeat separated by 4 nucleotides (DR-4). The DR-4 serves as binding motif for nuclear receptors suggesting cross-talk between different transcription factors [20–22]. No sequence difference was observed, neither in the regulatory element, nor in any other position within the 2903 bp region of the promoter investigated when compared to the control *ABCD2* sequence.

ABCD2 segregation analysis in a X-ALD family with differently affected children

Sequencing the *ABCD2* coding region and the putative promoter region did not reveal any difference in brothers affected by different clinical phenotypes. Since we could not exclude the possibility of cryptic mutations (e.g. mutations in intronic regions), segregation analysis was performed. We used the microsatellite markers D12S331, D12S1029, D12S1048, AFMA106VD5 and D12S315 (Table 2) comprising a genomic region of about 3133 kb (NCBI Map Viewer; www.ncbi.nlm.nih.gov/mapview) close to *ABCD2*. Segregation analysis disclosed that the patient presenting the (mild) Addison-only-phenotype at age of 20 (II-9, Fig. 1) had identical *ABCD2* alleles (A_1a_4) compared to his brother who had died form cerebral X-ALD at the age of 13 years (II-3, Fig. 1). Thus, no correlation between a specific X-ALD phenotype and a characteristic *ABCD2* allele distribution could be observed. Interestingly, there is a discrepancy in the fragment length of marker D12S1029 if the maternal A_1 allele as compared to the A_1 alleles of all brothers examined. This suggests a maternal somatic germline mutation.

Association study of ABCD2 SNPs and clinical phenotypes in X-ALD

In two independent studies the SNPs rs11172566 and rs11172661 were investigated in unrelated X-ALD patients and controls (Table 3). Both analyses revealed no evidence of the polymorphisms to be associated with X-ALD in general, nor with a severe (cerebral) or mild (noncerebral) phenotype, not even in the second study analyzing well characterized "extreme" phenotypes.

Discussion

The unpredictable variability of clinical courses of X-ALD has been a matter of speculation for a long time. There is no general correlation between the type of *ABCD1* gene mutation and the clinical phenotype. Although it cannot be excluded that residual ALDP transport activities (over the peroxisomal membrane) in individual ALDP-mutations, might prevent the development of the inflammatory cerebral form in X-ALD this would only explain the clinical manifestation in a small set of patients. Strikingly different clinical phenotypes can occur (i) in one nuclear family; (ii) in patients affected by mutations that lead to a complete absence of ALDP (e.g. large deletions); (iii) in unrelated families with the identical *ABCD1* mutation (e.g. 1801delAG); (iv) in monozygotic twins [3]. These findings in addition to genome wide association studies predict genetic and environmental factors to influence phenotypic heterogeneity in X-ALD.

Several candidate genes have been suggested as potential modifiers: peroxisomal ABC-half transporters related to ABCD1 (ABCD2, ABCD3); Very long chain fatty acid elongation (ELOVL1-6 [23]) and activation system (ACSVL1 and BG1 [24,25]); genes related to initiation or maintenance of inflammation (CD1A-E, HLA-locus, TNFα, MOG [26–30]) and cystathionine beta-synthase involved in the methionine metabolism [31,32]. It is tempting to speculate that more than one genetic variation might modulate the X-ALD phenotype.

We had hypothesized that the *ABCD2* gene could be such a modifier. There was good evidence since *ABCD2* is able to compensate for the loss of *ABCD1 in vivo* and *in vitro*. However, our combined data of sequence analysis, segregation analysis, and polymorphism association studies may be regarded as evidence against the hypothesis that *ABCD2* is a modifier gene contributing to the clinical heterogeneity in X-ALD. Nevertheless, a genetically distant locus that influences *ABCD2* expression and thus contributes to clinical variations was not excluded by our methodology. Regulation of *ABCD2* transcription is recognized to be exceptionally complex and can be modulated by a variety of nuclear receptors. However, in a recent study it was demonstrated that the expression levels of *ABCD2* in the normal-appearing white matter of brains derived from patients displaying different X-ALD phenotypes were similar and did not differ significantly from the levels observed in age-matched controls [25]. Therefore, the existence of a distant locus that influences *ABCD2* expression is unlikely in this sample. Likewise, epigenetic factors, such as methylation might influence the expression of *ABCD2* in X-ALD patients and cannot be excluded by our methodology. The promoter of the *ABDC2* gene, however, does not contain a high content of GC-sites (40%). Together with the observation of similar expression levels of *ABCD2* in brain tissue of X-ALD patients and controls, this renders differences in methylation to occur unlikely.

As ABCD2 can compensate ABCD1 deficiency, major attempts have been undertaken to get insights on the complex regulation of *ABCD2* gene expression with the final aim to pharmacologically induce the *ABCD2* gene expression in cell types where the loss of ABCD1 contributes to the progression of the disease in order to ameliorate the severity of the disease. The reported data may not be regarded as evidence for *ABCD2* to be a modifier gene in X-ALD, but since a functional *ABCD2* gene is prerequisite for therapeutic interventions, the finding of an intact *ABCD2* gene in all phenotypes of X-ALD sets an additional basis toward the aim of pharmacological surrogate gene therapy in X-ALD.

Table 3
Association studies of polymorphism (c.2614A → G) within the 3′UTR of the *ABCD2* gene

rs11172566	Patients (*n*)	AA (%)	AG (%)	GG (%)	Alleles (*n*)	A (%)	G (%)
ccALD	17	15 (88)	2 (12)	0	34	32 (94)	2 (6)
X-ALD non cerebral	28	25 (89)	3 (12)	0	56	53 (95)	3 (5)
Normal population	147	131 (89)	15 (10)	1 (<1)	294	277 (94)	17 (6)
rs11172661	Patients (*n*)	GG (%)	AG (%)	AA (%)	Alleles (*n*)	G (%)	A (%)
ccALD	44	26 (59)	15 (34)	3 (7)	88	67 (76)	21 (24)
"pure" AMN	28	21 (75)	6 (21)	1 (4)	56	48 (86)	8 (14)
Normal population	200	131 (66)	62 (31)	7 (4)	400	324 (81)	76 (19)

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