Figure S1. Family pedigrees segregating ADSL deficiency. Three families, described in the main text, are shown.

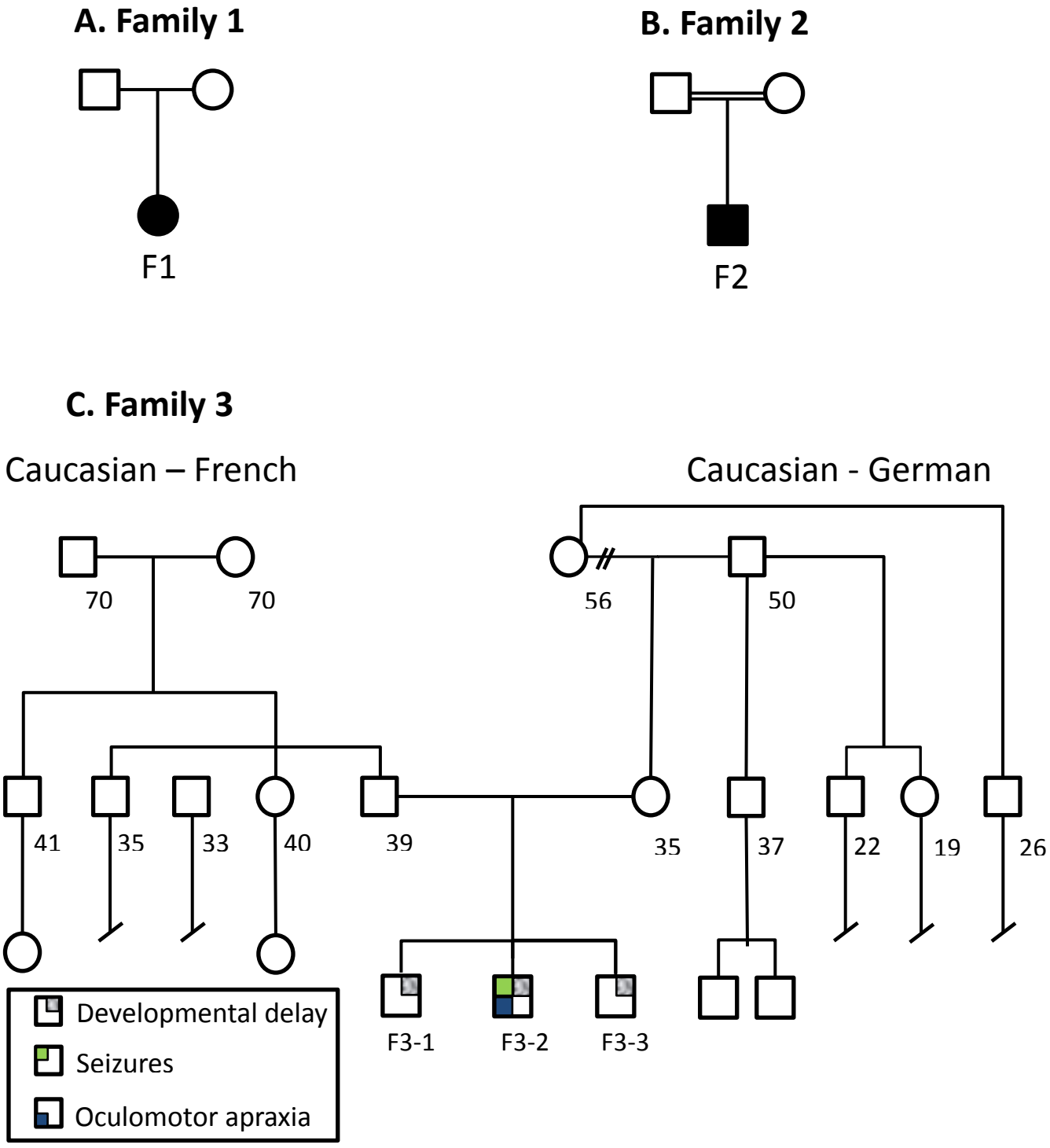

Table S1. Metabolomic profiling. Analytes with significant Z scores are shown. Patients F1, F2 and F3-2 have metabolomic profiling of plasma. Metabolomic profiling of urine of patient F1 and CSF of patient F2 are also provided.

F1 (Plasma)		**F1 (urine)**	
Biochemical	**z score**	**Biochemical**	**z score**
N6-succinyladenosine	7.66	N6-succinyladenosine	8.43
threitol	2.13	mandelate	3.25
N-acetylaspartate (NAA)	2.05	fucose	3.10
1-stearoyl-GPC (18:0)	-2.00	hydroquinone sulfate	2.94
3-methyl-2-oxobutyrate	-2.09	xylose	2.67
4-methyl-2-oxopentanoate	-2.09	adenosine	2.61
indolebutyrate	-2.18	2-oxo-1-pyrrolidinepropionate	2.43
2-linoleoyl-GPE* (18:2)*	-2.18	fucitol	2.29
1-linoleoyl-GPE (18:2)*	-2.22	4-allylphenol sulfate	2.21
1-arachidoyl-GPC (20:0)	-2.22	benzoate	2.17
1-oleoyl-GPI (18:1)*	-2.27	quinate	2.17
cysteine	-2.49		
indole-3-carboxylic acid	-2.50		
docosatrienoate (22:3n3)	-2.53		
alpha-ketobutyrate	-2.72		
propionylglycine (C3)	-2.98		

F2 (Plasma)		**F2 (CSF)**	
Biochemical	**z score**	**Biochemical**	**z score**
N6-succinyladenosine	9.46	N6-succinyladenosine	11.07
2-pyrrolidinone	7.44	adenosine	4.89
4-guanidinobutanoate	4.86	guanosine	3.78
erucate (22:1n9)	3.69	3-hydroxy-3-methylglutarate	3.27
arachidate (20:0)	2.71	N-acetylglutamine	2.78
C-glycosyltryptophan	2.64	myo-inositol	2.65
2-oleoylglycerol (18:1)	2.63	cytidine	2.57
glycohyocholate	2.59	3-methylglutaconate	2.45
1-oleoylglycerol (18:1)	2.39	galactitol (dulcitol)	2.28
N-carbamoylalanine	2.37	isovalerate (C5)	2.27
1,5-anhydroglucitol (1,5-AG)	2.36	β-hydroxyisovaleroylcarnitine	2.25
3-hydroxy-3-methylglutarate	2.35	N-acetylvaline	2.25
galactonate	2.29	argininosuccinate	2.24
hyocholate	2.27	orotidine	2.23
betaine	2.22	gulonic acid*	2.21
2,3-diphosphoglycerate	2.20	2-methylbutyroylcarnitine (C5)	2.20
methionine	-2.02	glucose	2.20
dehydroisoandrosterone sulfate (DHEA-S)	-2.03	phenyllactate (PLA)	2.16
tyrosine	-2.11	N-acetyl-beta-alanine	2.09
3-(4-hydroxyphenyl)lactate (HPLA)	-2.13	malonylcarnitine	2.07
valine	-2.16	C-glycosyltryptophan	2.04
2-aminobutyrate	-2.19	citramalate	-2.09
gamma-CEHC	-2.23	N-acetylglycine	-2.12
homoarginine	-2.23	1-oleoylglycerol (18:1)	-2.33
isobutyrylcarnitine (C4)	-2.26	N1-methyl-2-pyridone-5-carboxamide	-2.48
citrulline	-2.41	isocitrate	-2.86
isovalerylcarnitine (C5)	-2.72	1-palmitoylglycerol (16:0)	-3.87
p-cresol sulfate	-2.77		
urea	-2.77		
phenylalanine	-3.56		

F3-2 (Plasma)	
Biochemical	**z score**
N6-succinyladenosine	7.29
2-palmitoyl-GPE* (16:0)*	3.14
phenylacetylglycine	2.39
1-dihomo-linolenoyl-GPE (20:3n3 or 6)*	2.37
orotate	2.35
dimethylglycine	2.27
isovalerylglycine	2.03
tyrosine	2.01
butyrylcarnitine (C4)	-2.22
3-methoxytyrosine	-3.99

Table S2. Data from ExAc for c.1277G>A, p.Arg426His variant.

Chromosome	22
Position	40760969
RSID	rs119450941
Reference	G
Alternate	A
Consequence	p.Arg426His
Protein Consequence	p.Arg426His
Transcript Consequence	c.1277G>A
Annotation	missense
Allele Count	31
Allele Frequency	0.0002553
Allele Count African	1
Allele Count East Asian	0
Allele Count European (Non-Finnish)	28
Allele Count Finnish	0
Allele Count Latino	1
Allele Count Other	0
Allele Count South Asian	1

Data accessed http://exac.broadinstitute.org on 05052016.

Table S3. ExAc data for other pathogenic alleles reported in the literature.

	Variant	Allele Count	Allele Frequency
1	del206-218	na	na
2	t-49c	na	na
3	p.Met1Leu	na	na
4	p.Met1Val	na	na
5	p.Ala2Val	12	0.0001812
6	p.Ala3Val	na	na
7	p.Ala3Pro	na	na
8	p.Met26Ile	2	0.00002106
9	p.Ile72Val	na	na
10	p.Glu80Asp	na	na
11	p.Asp87Glu	na	na
12	p.Pro100Ala	1	0.000008238
13	p.Tyr114His	5	0.0000412
14	p.Arg141Trp	2	0.00001647
15	p.Arg190Gln	8	0.00006591
16	p.Arg190Ter	1	0.000008238
17	p.Arg194Cys	na	na
18	p.Lys246Glu	na	na
19	p.Asp268Asn	3	0.00002471
20	p.Arg303Cys	5	0.00004119
21	p.Leu311Val	na	na
22	p.Pro318Leu	3	0.00002472
23	p.Arg337X	na	na
24	p.Val364Met	1	0.00000824
25	p.Arg374Trp	2	0.00001674
26	p.Ser395Arg	na	na
27	p.Arg396cys	na	na
28	p.Arg396His	6	0.00005192
29	p.Asp422Tyr	2	0.00001647
30	p.Leu423Val	na	na
31	**p.Arg426His**	**31**	**0.0002553**
32	p.Asp430Asn	2	0.00001647
33	p.Ser438Pro	na	na
34	p.Ser447Pro	2	0.00001647
35	p.Ser448Pro	1	0.000008236
36	p.Thr450Ser	5	0.00004118
37	p.Arg452Pro	na	na
38	p.Pro467Arg	na	na

Data accessed http://exac.broadinstitute.org on 05052016.
na – not available in ExAc