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Supplementary Files

Prospective Evaluation of Kidney Disease in Joubert Syndrome.

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Supplementary Methods

Molecular Genetics Methods

The 27 JS genes sequenced by combining a MIP capture method and next-generation sequencing were *AHI1, ARL13B, B9D1, B9D2, C2CD3, C5orf42, CC2D2A, CEP290, CEP41, CSPP1, IFT172, INPP5E, KIF7, MKS1, NPHP1, OFD1, RPGRIP1L, TCTN1, TCTN2, TCTN3, TMEM138, TMEM216, TMEM231, TMEM237, TMEM67, TTC12B* and *ZNF423*.(1) Whole exome sequencing performed using the HiSeq2000 (Illumina, San Diego, CA) employed 101-bp paired-end read sequencing. Confirmatory Sanger sequencing of gDNA and cDNA was performed as described. The molecular genetic diagnosis was made based on the identification of variants in the known genes if one or more of the following criteria were met: 1. Two null alleles in a gene associated with JS, 2. Both alleles with variants previously reported to cause JS, 3. One allele with a variant previously reported to cause JS and another null allele, 4. One null allele and a variant predicted to be deleterious (PolyPhen2, CADD and Sift), 4. One allele with a variant previously reported to cause JS and a variant predicted to be deleterious (PolyPhen2, CADD and Sift) 5. Both alleles with variants predicted to be deleterious (PolyPhen2, CADD and Sift) and MAF <0.0001 (ExAC).

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1. Vilboux T, Doherty DA, Glass IA, Parisi MA, Phelps IG, Cullinane AR, Zein W, Brooks BP, Heller T, Soldatos A, Oden NL, Yildirimli D, Vemulapalli M, Mullikin JC, Nisc Comparative Sequencing P, Malicdan MC, Gahl WA, Gunay-Aygun M: Molecular genetic findings and clinical correlations in 100 patients with Joubert syndrome and related disorders prospectively evaluated at a single center. *Genetics in medicine : official journal of the American College of Medical Genetics*, 2017

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Table 1S. Molecular Genetic and Main Clinical Findings of 97 Joubert Sydrome Patients Evaluated at the NIH Clinical Center.

Patient No	Family No	NIH Ciliopathyt No	Gender	Age	Gene	Mutation 1	Mutation 2	Polydactyly	Coloboma	Retinal Dystrophy	Liver Disease	Kidney Disease
1	1	361	m	0.9	TMEM67	c.1538A>G; p.(Tyr513Cys)	c.2122G>A; p.(Ala708Thr)	-	+	-	+	-
2	2	545	f	2.2	TMEM67	c.622A>T; p.(Arg208*)	c.2140_2142del; p.(Ser715del)	-	-	-	+	-
3	3	97	m	3.9	TMEM67	c.755T>C; p.(Met252Thr)	c.1843T>C; p.(Cys615Arg)	-	+	-	-	+
4	4	548	m	4.5	TMEM67	c.748G>A, p.(Gly250Arg)	c.2879C>T; p.(Ala960Val)	-	+	-	+	+
5	5**	216	f	4.9	TMEM67	c.2522A>C; p.(Gln841Pro)	c.622A>T; p.(Arg208*)	-	+	-	+	+
6	6	302	m	5.1	TMEM67	c.2802delA; p.(Asn935Metfs*25)	Not identified	-	+	-	+	-
7		301	m	9.5	TMEM67	c.2802delA; p.(Asn935Metfs*25)	Not identified	-	+	-	+	-
8	7	271	f	6.7	TMEM67	c.1843 T>C; p.(Cys615Arg)	c.1843 T>C; p.(Cys615Arg)	-	-	-	+	+
9		272	m	9.3	TMEM67	c.1843 T>C; p.(Cys615Arg)	c.1843 T>C; p.(Cys615Arg)	-	-	-	+	+
10	8	557	m	6.8	TMEM67	c.579_580del; p.(Gly195Ilefs*13)	c.950C>G; p.(Thr317Arg)	-	+	-	+	+
11		559	m	16.7	TMEM67	c.579_580del; p.(Gly195Ilefs*13)	c.950C>G; p.(Thr317Arg)	-	+	-	+	+
12	9	459	f	7.8	TMEM67	c.1081G>T; p.(Glu361*)	c.2661+5G>A	-	+	-	+	-
13	10	238	m	8.2	TMEM67	c.224-2 A>T	c.1843 T>C; p.(Cys615Arg)	-	-	-	+	+
14	11	255	m	9	TMEM67	c.297G>T; p.(Lys99Asn)	c.2322+2dup	-	+	-	+	-
15	12	542	f	11.9	TMEM67	c.1538 A>G; p.(Thr513Cys)	c. 2498 T>C; p.(Ile833Thr)	-	+	-	+	-
16	13	303	f	14.7	TMEM67	c. 2498 T>C; p.(Ile833Thr)	c.1351C>T; p.(Arg451*)	-	+	-	+	+
17	14**	252	f	14.8	TMEM67	c.1674+3A>G	c.1126C>G; p.(Gln376Glu)	-	+	-	+	+
18	15	309	m	17.4	TMEM67	c.769A>G; p.(Met257Val)	Not identified	-	+	-	+	+
19	16	562	m	22.9	TMEM67	c.755T>C; p.(Met252Thr)	c.245C>G; p.(Pro82Arg)	-	+	-	+	-
20		561	m	24.9	TMEM67	c.755T>C; p.(Met252Thr)	c.245C>G; p.(Pro82Arg)	-	+	-	+	-
21		560	m	29.6	TMEM67	c.755T>C; p.(Met252Thr)	c.245C>G; p.(Pro82Arg)	-	+	-	+	-
22	17	432	f	36.2	TMEM67	c.2322+2dup	c.2661+5G>A	-	+	+	+	-
23	18	488	m	0.6	C5orf42	c.7988_7989del; p.(Gly2663Alafs*40)	c.7988_7989del; p.(Gly2663Alafs*40)	-	-	-	-	-
24		487	f	5.3	C5orf42	c.7988_7989del; p.(Gly2663Alafs*40)	c.7988_7989del; p.(Gly2663Alafs*40)	-	-	-	-	-
25	19	355	f	2.1	C5orf42	c.1784T>G; p.(Leu595*)	c.5348C>A; p.(Ala1783Asp)	-	-	-	-	-
26	20	458	f	2.2	C5orf42	c.1819del; p.(Tyr607Thrfs*6)	Not identified	-	-	-	-	-
27	21	523	f	2.3	C5orf42	c.510dup; p.(Leu171Serfs*8)	c.8710C>T; p.(Arg2904*)	-	-	-	+	-
28	22	471	m	8	C5orf42	c.1819del; p.(Tyr607Thrfs*6)	c.7817T>A; p.(Leu2606*)	+	-	-	-	-
29	23	534	f	8.4	C5orf42	c.2999G>T; p.(Trp1000Leu)	c.3001A>G; p.(Thr1001Ala) and c.8855+1G>A	-	+	-	-	-
30	24	501	m	10	C5orf42	c.7190del; p.(Pro2397Glnfs*37)	c.8710C>T; p.(Arg2904*)	+	-	-	+	-
31		500	f	11.8	C5orf42	c.7190del; p.(Pro2397Glnfs*37)	c.8710C>T; p.(Arg2904*)	+	-	-	+	-
32	25	404	m	10.3	C5orf42	c.2923C>T; p.(Gln975*)	c.8710C>T; p.(Arg2904*)	-	-	-	-	-
33	26	568	f	14.1	C5orf42	c.5737+2T>C	c.2624C>T; p.(Ser875Phe)	-	-	-	-	-
34	27	528	m	18.8	C5orf42	c.455C>T; p.(Ser152Phe)	c.2334G>A; p.(Trp778*)	-	-	-	+	-
35	28	491	m	19	C5orf42	c.7477C>T; p.(Arg2493*)	c.8263dup; p.(Thr2755Asnfs*8)	-	-	-	-	-
36	29	482	f	24.5	C5orf42	c.1784T>G; p.(Leu595*)	c.8263_8264insG; p.(Thr2755Serfs*8)	+	-	-	+	-
37		481	m	27.6	C5orf42	c.1784T>G; p.(Leu595*)	c.8263_8264insG; p.(Thr2755Serfs*8)	+	-	-	+	-
38	30	378	f	1.8	CC2D2A	c.3975+4_3975+7del	c.4667A>T; p.(Asp1556Val)	-	-	-	+	-
39	31	483	f	2.3	CC2D2A	c.248-4_248-3insAAGTTTT	c.3452T>C; p.(Val1151Ala)	-	-	-	-	-
40	32	575	f	2.3	CC2D2A	c.3289del; p.(Val1097Phefs*2)	c.4667A>T; p.(Asp1556Val)	-	-	-	-	+
41	33	495	m	3.5	CC2D2A	c.4741A>G; p.(Thr1581Ala)	c.3347C>T; p.(Thr1116Met)	-	-	-	-	-

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42	34**	446	m	3.2	CC2D2A	c.3289del; p.(Val1097Phefs*2)	c.3851G>A; p.(Arg1284His)	+	+	-	-	-
43	35	185	m	3.6	CC2D2A	c.3145C>T; p.(Arg1049*)	c.3347C>T; p.(Thr1116Met)	-	-	-	+	+
44	36	577	f	13.1	CC2D2A	c.3743_3746dup; p.(Pro1250Glyfs*11)	c.3989G>A; p.(Arg1330Gln)	-	-	-	-	-
45		576	f	15.7	CC2D2A	c.3743_3746dup; p.(Pro1250Glyfs*11)	c.3989G>A; p.(Arg1330Gln)	-	-	-	-	-
46	37	565	f	15.4	CC2D2A	c.1017+1G>A	c.4600T>G; p.(Leu1534Val)	-	-	+	+	-
47	38	364	f	16.3	CC2D2A	c.3055C>T; p.(Arg1019*)	c.3288G>C; p.(Gln1096His)	-	-	-	-	-
48	39	480	m	0.9	CEP290	c.5182G>T; p.(Glu1728*)	c.5668G>T; p.(Gly1890*)	-	-	-	-	+
49	40	552	m	4.3	CEP290	c.4723A>T; p.(Lys1575*)	c.4966G>T; p.(Glu1656*)	-	-	+	-	+
50	41	373	m	4.4	CEP290	c.4882C>T; p.(Gln1628*)	c.6072C>A; p.(Tyr2024*)	-	-	+	+	+
51	42	455	m	6.9	CEP290	c.1623+1G>A	c.5668G>T; p.(Gly1890*)	-	-	+	-	-
52	43	412	m	10	CEP290	c.1666dup; p.(Ile556Asnfs*20)	c.5344C>T; p.(Arg1782*)	-	-	+	-	+
53	44**	213	f	13.2	CEP290	c.5611_5614del; p.(Gln1871Valfs*2)	c.4882C>T; p.(Gln1628*)	-	+	+	-	+
54	45	441	f	23.5	CEP290	c.5668G>T; p.(Gly1890*)	c.5356_5571del; p.(Glu1786_Leu1857del)	-	+	+	-	+
55	46	513	m	1.9	AHI1	c.1997A>T; p.(Asp666Val)	c.2297G>A; p.(Gly766Glu)	-	-	-	-	-
56	47	517	m	3.3	AHI1	c.662C>A; p.(Ser221*)	c.1583C>G; p.(Ser528*)	-	-	+	+	+
57	48	472	m	5	AHI1	c.1976A>T; p.(Asp659Val)	c.2212C>T; p.(Arg738*)	-	-	+	-	-
58	49	574	m	5.1	AHI1	c.910dup; p.(Thr304Asnfs*6)	c.2105C>T; p.(Thr702Met)	-	-	+	-	-
59	50	540	f	17.9	AHI1	c.1115A>G; p.(Asp372Gly)	c.2173T>C; p.(Trp725Arg)	-	-	+	+	+
60	51	228	f	20.9	AHI1	c.736A>T; p.(Lys246*)	c.2495T>G; p.(Leu832*)	-	-	+	+	+
61	52	443	f	2.2	KIAA0586	c.392del; p.(Arg131Lysfs*4)	c.1254-1G>C	-	-	-	-	-
62	53	368	m	4	KIAA0586	c.392del; p.(Arg131Lysfs*4)	c.1000C>T; p.(Gln334*)	-	+	-	-	-
63	54	494	m	4.4	KIAA0586	c.94dup; p.(His32Profs*8)	c.586-350_1129+1117del	-	+	-	-	-
64	55	579	m	4.4	KIAA0586	c.392del; p.(Arg131Lysfs*4)	c.586-350_1129+1117del	-	-	-	-	-
65	56	507	m	4.7	KIAA0586	c.831C>T; p.(Leu277Leu)	c.586-350_1129+1117del	-	-	-	-	-
66	57	531	m	13.6	KIAA0586	c.392del; p.(Arg131Lysfs*4)	c.961+1G>A	-	-	-	-	-
67	58	502	m	1.5	MKS1	c.1389G>T; p.(Arg463Arg)	c.493C>T; p.(Arg165Cys)	-	-	-	-	-
68	59	397	m	1.7	MKS1	c.950G>A; p.(Gly317Glu)	c.1115_1117del; p.(Ser372del)	+	-	+	-	-
69	60	537	m	2	MKS1	c.417G>A; p.(Glu139Glu)	c.1476T>G; p.(Cys492Trp)	+	-	+	+	-
70	61	510	m	8	MKS1	c.1408-36_1408-6del	c.1387C>G; p.(Arg463Gly)	-	-	+	-	-
71	62	573	m	14	MKS1	c.417G>A; p.(Glu139Glu)	c.1208C>T; p.(Ser403Leu)	-	-	+	-	-
72	63	372	m	3.2	INPP5E	c.473delG; p.(Gly158Valfs*40)	c.1304G>A; p.(Arg435Gln)	-	+	+	-	+
73	64	352	m	14.5	INPP5E	c.1784_1787del; p.(Val595Glyfs*21)	c.1862G>A; p.(Arg621Gln)	-	-	+	+	+
74	65	7504	f	19	INPP5E	c.1565G>C; p.(Gly522Ala)	c.1565G>C; p.(Gly522Ala)	-	-	+	-	-
75		7503	f	21	INPP5E	c.1565G>C; p.(Gly522Ala)	c.1565G>C; p.(Gly522Ala)	-	-	+	-	-
76	66¥	520	f	1.2	TMEM231	c.712G>A; p.(Asp238Asn)	g.18555_19148conNG_026383.1:g.2718_3301; p.(Ile224Leufs*5)	-	-	-	+	-
77		518	f	4.8	TMEM231	c.712G>A; p.(Asp238Asn)	g.18555_19148conNG_026383.1:g.2718_3301; p.(Ile224Leufs*5)	-	-	+	-	-
78		519	f	4.8	TMEM231	c.712G>A; p.(Asp238Asn)	g.18555_19148conNG_026383.1:g.2718_3301; p.(Ile224Leufs*5)	-	-	+	-	-
79	67	438	m	3.4	NPHP1	290 kb common deletion	290 kb common deletion	-	-	-	-	+
80	68	396	f	9	TMEM216	c.218G>T; p.(Arg73Leu)	c.253C>T; p.(Arg85*)	+	-	-	+	+
81	69	408	m	12	TMEM216	c.218G>T; p.(Arg73Leu)	c.218G>T; p.(Arg73Leu)	+	+	-	-	-
82	70	3331	m	4.3	OFD1	c.2656del; p.(Gln886Lysfs*2)	Not applicable as X-linked	-	-	+	-	-
83	71	452	m	12.3	OFD1	c.149A>G; p.(His50Arg)	Not applicable as X linked	-	-	-	+	-
84	72	466	f	2.3	CSPP1	c.2244_2245del; p.(Glu750Glyfs*30)	c.2280del; p.(Glu761Lysfs*35)	-	-	+	-	-
85	73	387	f	3.5	CSPP1	c.1835_1845del; p.Arg612Thrfs*2	c.2814-1G>C	-	-	-	-	-
86	74	409	m	2.1	KIF7	c.3505C>T; p.(Gln1169*)	c.3505C>T; p.(Gln1169*)	-	-	-	-	-
87	75	400	m	4.8	B9D1	c.95A>G; p.(Tyr32Cys)	c.466C>T; p.(Arg156Trp)	-	-	-	-	-
88	76	360	m	21.4	RPGRIP1L	c.671_677del; p.(Glu224Glyfs*7)	c.1340T>C; p.(Leu447Ser) and c.3790G>T; p.(Asp1264Tyr)	+	+	-	-	+
89	77	474	f	4.5	TMEM237	c.76C>T; p.(Gln26*)	c.943+1G>T	-	+	+	-	+
90	78	390	f	1.9	KIAA0753	c.769A>G; p.(Arg257Gly)	c.2359-1G>C	-	-	-	-	-

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91	78	389	m	7	KIAA0753	c.769A>G; p.(Arg257Gly)	c.2359-1G>C	-	-	-	-	-
92	79	449	f	7.9	CELSR2	c.1150G>A; p.(Ala384Thr)	c.6908C>T; p.(Thr2303Met)	-	-	-	+	-
93	80	393	m	1.7	Unknown	Not identified	Not identified	+	+	-	+	-
94	81	578	f	2.3	Unknown	Not identified	Not identified	-	+	-	-	-
95	82	570	m	4.7	Unknown	Not identified	Not identified	-	-	-	-	-
96	83	419	f	2	Unknown	Not identified	Not identified	-	-	+	-	-
97	84	358	m	9.1	Unknown	Not identified	Not identified	-	-	-	+	+

Patients are grouped by gene and within each gene patients are sorted from the youngest to oldest. **These 4 families had history of an affected deceased sibling. ¥This family had a stillborn son with polycystic kidneys after their evaluation at NIH.