Supplementary Material

Haploinsufficiency of the *SUFU* gene cause a recognizable neurodevelopmental phenotype at the mild end of Joubert syndrome spectrum

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Supplementary Table 1 - Clinical features (European cohort)

Family code	**COR 206**	**COR 269**		**COR 280**					**COR 552**		**COR 572**		**CCM 667**	**OPBG-136**	**Vienna family**		**COR537**		**COR599**
cDNA c.	1194_1195del	895C>T		846dup					1022+1G>A		846dup		71dup	757G>T	71del		37_53del		1145del
protein p.	S399Yfs*4	R299*		E283Rfs*3					splice		E283Rfs*3		A25Gfs*23	E253*	P24Rfs*72		T13Wfs*29		P382Lfs*4
segregation	de novo	maternal		maternal					maternal		not tested		*de novo*	*de novo*	maternal		paternal		de novo
Subjects	NG 2282	NG 2526	NG 2527	NG 2721	NG 2724	15045	15043	NG 2723	NG 5499	NG 5748	NG 5723	NG 5866	NG 5993	OPBG-136	B3515	B6284	NG 5426	NG 6227	NG 6191
Relation with proband	prob	prob	moth	prob	sib	sib	sib	moth	prob	moth	prob	sib	prob	prob	prob	moth	prob	fath	prob
Age	10-15y	10-15y	40-45y	15-20y	10-15y	10-15y	5-10y	40-45y	5-10y	30-35y	5-10y	5-10y	0-5y	5-10y	5-10y	40-45y	5-10y	50-55y	0-5y
Sex	M	M	F	M	F	M	M	F	M	F	M	M	M	F	M	F	F	M	M
Referral diagnosis for genetic test	poss. JS	JS	NA	poss. JS	poss. JS	poss. JS	poss. JS	NA	JS	NA	poss. JS	poss. JS	poss. JS MaC	COMA	COMA	NA	JS	NA	JS
infantile hypotonia	no	yes	no	no	no	no	no	no	yes	no	yes	yes	yes	yes	yes	no	yes	no	yes
abnormal breathing	yes	no	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	no	no	no
sitting	9m	9m	8m	7m	6m	7m	6m	norm	24m	8m	9m	7m	8m	8m	12m	norm	8m	6m	8m
independent walking	21m	30m	18m	19m	18m	18m	18m	norm	6y	18m	36m	24m	22m	24m	24m	norm	14m	14m	no
speech delay	no	no	no	no	yes	no	no	no	yes	no	yes	yes	yes	yes	yes	no	yes	no	-
persistent COMA	yes	yes	no	yes	yes	yes	yes	no	yes	no	yes	yes	yes	yes	yes	no	yes	no	yes
mild ataxia	no	yes	yes	no	no	no	no	no	yes	no	yes	yes	yes	yes	yes	no	no	no	-
*macrocephaly**	yes	no	no	yes	yes	yes	yes	no	yes	no	no	no	yes	yes	yes	no	frontal bossing	no	yes
ID	no	no	no	no	no	no	no	no	mod	no	sev	sev	mild	mild	mild	no	no	no	-
Education	MS	MS	MS	MS	MS	MS	MS	MS	SAS	MS	SAS	SAS	-	MS	SAS	MS	SAS	MS	-
Other features	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no	bicuspid valve insuff.

Legend: COMA, congenital ocular-motor apraxia; fath, father; ID, intellectual disability, JS, Joubert syndrome; m, months; MaC, macrocerebellum; mod, moderate; moth, mother; MTS, molar tooth sign; NA, not applicable; norm: exact age could not be remembered but reported as normal; poss. JS: possible JS (reported by referring clinicians/neuroradiologists with variable terminology [JS-like, mild JS, mild MTS, JS spectrum], as they featured some clinical and/or imaging features suggestive of JS but not sufficient to reach a definite diagnosis); prob, proband; sev, severe; y, years. *includes parental report of “large head”, even if not proven >98

percentile. For education: MS, mainstream school; SAS, school attendance with support. Clinically asymptomatic carrier parents are shaded in blue. Raw data available at 10.5281/zenodo.5502747.

Supplementary Table 2 - Clinical features (US cohort)

Family	**UW-422**	**UW423-UW427**				**UW435**	**UW463**	**UW430**		**UW464**	**UW465**
cDNA c.	1294C>T	304del				1258G>T	1158-1G>A	1157+3G>A		1023-2A>C	23_29del
protein p.	Q432*	N102Tfs*19				E420*	splice	splice		splice	G8Afs*86
segregation	*de novo*	both paternal				not tested	*de novo*	paternal		*de novo*	*de novo*
Subjects	UW422-3	UW423-3	UW423-1	UW427-3	UW427-1	UW435-3	UW463-3	UW430-3	UW430-1	UW464-3	UW465-3
Relation with proband	prob	prob	fath	cousin (son of UW427-1)	cousin of UW423-1	prob	prob	prob	fath	prob	prob
Age	10-15y	5-10y	35-40y	5-10y	40-45y	5-10y	5-10y	5-10y	35-40y	20-25m	5-10y
Sex	M	M	M	M	M	M	M	M	M	M	M
Referral diagnosis for genetic test	poss. JS	COMA	-	COMA	-	COMA	poss. JS	COMA	-	poss. JS	poss. JS
infantile hypotonia	yes	yes	no	yes	no	yes	yes	yes	no	yes	yes
abnormal breathing	no	yes	no	no	no	yes	no	no	no	no	no
sitting	9m	12m	9-11m	9m	-	9m	18m	14m	7m	8m	6m
independent walking	20m	30m	12-15m	22m	-	21m	36m	30m	12m	no	14m
speech delay	no	no	no	no	no	no	no	no	no	-	yes
persistent COMA	yes	yes	no	yes	no	yes	yes	yes	no	yes	yes
mild ataxia	no	yes	no	yes	no	yes	yes	yes	no	no	yes
macrocephaly *	yes	yes	yes	yes	-	yes	yes	yes	yes	yes	yes
ID	no	no	no	no	no	no	no	mild	no	-	no
Education	MS	SAS	MS	MS	MS	MS	SAS	SAS	MS	-	SAS
Other features				postaxial polydactyly left foot		Type I laryngeal cleft, aplasia cutis, cafè au lait spots					

Legend: COMA, congenital ocular-motor apraxia; fath, father; ID, intellectual disability, JS, Joubert syndrome; m, months; MTS, molar tooth sign; poss. JS: possible JS (reported by referring clinicians/neuroradiologists with variable terminology [JS-like, mild JS, mild MTS, JS spectrum], as they featured some clinical and/or imaging features suggestive of JS but not sufficient to reach a definite diagnosis); prob, proband, y, years. *includes parental report of “larger head than average”, even if not proven >98 percentile. For education: MS, mainstream school; SAS, school attendance with support. Clinically asymptomatic carrier parents are shaded in blue. Raw data available at 10.5281/zenodo.5502747.

Supplementary Table 3 - Brain MRI features (European cohort)

Family	**COR 206**	**COR 269**		**COR 280**					**COR 552**		**COR 572**		**CCM 667**	**OPBG-136**	**Vienna family**		**COR537 COR537**		**COR599**
Subjects	NG 2282	NG 2526	NG 2527	NG 2721	NG 2724	15045	15043	NG 2723	NG 5499	NG 5748	NG 5723	NG 5866	NG 5993	OPBG-136	B3515	B6284	NG 5426	NG 6227	NG 6191
Relation with proband	prob	prob	moth	prob	sib	sib	sib	moth	prob	moth	prob	sib	prob	prob	prob	moth	prob	fath	prob
SCP horizontal	yes	yes	yes	yes	yes	yes	yes	yes	yes	-	yes	yes	yes	yes	yes	-	yes	no	yes
SCP long	yes	?	yes	yes	yes	yes	yes	yes	yes	-	yes	yes	yes	?	yes	-	yes	no	yes
SCP thick	yes	yes	yes	yes	yes	yes	yes	yes	yes	-	yes	yes	yes	yes	yes	-	yes	no	yes
Superior cerebellar dysplasia	yes	yes	yes	yes	yes	yes	yes	yes	yes	-	yes	yes	yes	yes	yes	-	yes	no	yes
Vermis hypoplasia	yes	yes	yes	yes	yes	yes	yes	yes	yes	-	yes	yes	yes	yes	yes	-	yes	no	yes
Vermian split	yes	yes	no	no	yes	yes	yes	no	no	-	yes	?	?	?	no	-	yes	no	yes
Fastigium displaced	yes	yes	no	yes	yes	no	no	no	no	-	no	no	no	no	no	-	yes	no	yes

Legend: SCP, superior cerebellar peduncles; ?, unable to assess due to image quality. Clinically asymptomatic carrier parents are shaded in blue.

Supplementary Table 4 - Brain MRI features (US cohort)

Family	**UW-422**	**UW423-UW427**				**UW435**	**UW463**	**UW430**		**UW464**	**UW465**
Subjects	UW422-3	UW423-3	UW423-1	UW427-3	UW427-1	UW435-3	UW463-3	UW430-3	UW430-1	UW464-3	UW465-3
Relation with proband	prob	prob	father	cousin (son of UW427-1)	cousin of UW423-1	prob	prob	prob	father	prob	prob
SCP horizontal	yes	yes	-	?	-	no	yes	yes	-	yes	yes
SCP long	no	yes	-	yes	-	no	yes	yes	-	yes	yes
SCP thick	no	yes	-	yes	-	no	yes	yes	-	no	yes
Superior cerebellar dysplasia	yes	yes	-	yes	-	yes	yes	yes	-	yes	yes
Vermis hypoplasia	yes	yes	-	yes	-	yes	yes	yes	-	yes	yes
Vermian split	yes	yes	-	?	-	yes	yes	yes	-	yes	yes
Fastigium displaced	yes	yes	-	yes	-	no	yes	yes	-	yes	yes

Legend: SCP, superior cerebellar peduncles; ?, unable to assess due to image quality. Clinically asymptomatic carrier parents are shaded in blue.