

SUPP. TABLE S1. Clinical features of subjects heterozygous for a germline *BRAF* gene mutation.

A: Angioma; AD: ascending aortic dilatation; AIS: aortic isthmus stenosis; AN: acanthosis nigricans; AP: advanced puberty; AS: asymmetric thelarche; B: brain atrophy; C: coloboma; CB: cortical blindness; CF: club feet; CFCS: cardiofaciocutaneous syndrome; CM1: Chiari malformation type 1; c.e.o. compatible with ethnic origin; DN: dystrophic nails; DP: delayed puberty; DS: dry skin ; EN: ependymal nodules; FD: fibrocystic dysplasia; FC: follicular ovarian cysts; FT: Fanconi tubulopathy; H: hernia; HCC: hypoplastic corpus callosum; IH: inguinal hernia; JC: large joint contractures; LP: lymphedema; LS: LEOPARD syndrome; M: macrostomia; MS: mitral stenosis; My: myopia; N: nystagmus; n.a. : data not available; n.app.: data not applicable; NS: Noonan syndrome; OFC: occipitofrontal circumference; PL: periventricular leukomalacia; PP: pes planus ; PUO: pyeloureteral obstruction ; S: strabismus; SS: soft skin; UT: undescended testis; VD: ventricular dilatation.

PATIENT CODE	N01	N02	N03	N04	N05	N06	N07	N08	N09	N10	N11	N12
Clinical diagnosis	LS	NS	NS	NS	NS	NS	CFCS	CFCS	CFCS	CFCS	CFCS	CFCS
Amino acid change	T241P	T241M	W531C	W531C	L597V	T241R	E275K	L245F	A246P	Q257R	G469E	L485F
Sex/age (yrs)	M/15.8	F/15.5	F/3.2	F/15.2	F/7.5	F/1.2	F/7.0	M/0.3	F/7	F/1.8	F/0.8	F/7

Polyhydramnios	no	no	no	no	no	no	yes	no	yes	yes	yes	yes
Fetal macrosomia	no	yes	no	no	n.a.	yes	n.a.	yes	no	yes	yes	yes
Birth weight (gr)/weeks	3400/40	4350/39	2500/34	2630/37	3610/38	3950/37	3330/30	4050/40	2300/33	3250/39	4050/39	3630/38
OFC at birth (cm)	35	35	32	34	36,2	35	34	35	33	n.a.	37	36
Neonatal growth failure	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Poor sucking	no	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no
Poor swallowing	no	yes	yes	yes	no	yes	yes	yes	yes	yes	no	yes
Tube feeding	no	yes	no	yes	no	no	yes	no	yes	yes	no	yes
Esophageal anomalies	no	no	yes	yes	no	no	yes	no	no	yes	no	yes
Short stature (<3rd centile)	yes	yes	Yes	yes	yes	yes	no	no	yes	yes	no	yes
Craniofacial anomalies	yes	yes	Yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Macrocephaly	yes	no	yes	no	yes	yes	yes	no	yes	yes	no	no
Dolicocephaly	yes	yes	yes	yes	no	yes	yes	no	no	yes	yes	no
Prominent forehead	yes	yes	no	yes	yes	yes	no	no	yes	yes	yes	yes
Bitemporal narrowing	yes	yes	no	yes	no	yes	yes	yes	no	yes	yes	no
Downslanting palpebral fissures	yes	yes	no	no	yes	yes	no	yes	yes	yes	no	no
Hypertelorism	yes	yes	yes	yes	yes	yes	no	yes	no	yes	yes	yes
Thick palpebral lids	yes	yes	no	no	no	yes	no	yes	no	yes	yes	no
Epicanthal folds	no	no	no	no	no	no	no	yes	no	yes	no	yes
Palpebral ptosis	yes	yes	no	no	yes	yes	yes	yes	yes	yes	yes	yes
Flat nasal bridge	no	no	yes	yes	no	yes	no	yes	yes	yes	yes	yes
Thick lips	yes	yes	no	no	no	yes	no	yes	no	yes	yes	no
Low-set ears with thickened helix	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes
Large thick ear lobe	no	yes	no	no	yes	no	no	yes	no	yes	no	yes
Prominent/pointed/receding chin	yes	yes	no	no	yes	no	yes	no	yes	yes	no	yes
Low posterior hairline	yes	yes	no	no	yes	no	yes	yes	yes	yes	no	no
Cardiac anomalies	yes	no	no	no	yes	yes	yes	yes	yes	yes	yes	yes
Hypertrophic cardiomyopathy	no	no	no	no	no	no	no	yes	yes	yes	yes	yes
Congenital heart defect	yes	no	no	no	yes	yes	yes	yes	yes	yes	yes	yes
Polyvalvular dysplasia	yes	no	no	no	no	no	no	no	no	no	no	no
Pulmonary valve stenosis	no	no	no	no	no	yes	yes	yes	yes	yes	no	no
Pulmonary valve dysplasia	no	no	no	no	no	yes	n.a.	yes	no	no	no	no
Mitral valve dysplasia	yes	no	no	no	no	no	no	no	no	no	yes	no
Supravalvular pulmonary stenosis	no	no	no	no	no	yes	no	yes	no	no	no	no
Atrial septal defect	no	no	no	no	yes	no	no	yes	no	no	no	no
Other	no	no	no	no	no	no	no	no	no	MS, AIS	no	no
ECG anomalies/arrhythmias	no	no	no	no	no	no	no	yes	no	no	no	no
Ectodermal anomalies	yes	yes	yes	yes	no	no	yes	yes	yes	yes	yes	yes
Absent/hypoplastic eyebrows	no	no	no	no	no	no	yes	Yes	yes	yes	yes	yes
Curly hairs	yes	yes	no	no	c.e.o.	no	yes	no	yes	no	no	yes
Sparse hair	no	no	no	no	no	no	no	yes	yes	yes	yes	yes
Hyperkeratosis	yes	no	no	no	no	no	yes	no	no	yes	yes	no
Keratosis pilaris	no	no	no	no	n.a.	no	n.a.	no	no	yes	yes	yes
Hyperhidrosis	n.a.	n.a.	yes	no	n.a.	n.a.	n.a.	n.a.	no	yes	yes	yes
Deep palmar/plantar creases	no	no	yes	no	no	no	no	no	no	yes	no	no
Dark skin pigmentation	no	no	no	no	no	no	no	no	yes	no	yes	yes
Naevi (number)	yes	yes	no	yes	no	no	no	no	no	no	no	no
Cafè au lait spots	2	no	no	no	no	no	no	no	no	no	2	no
Lentigo (number)	>40	>40	3	>20	no	no	no	no	no	no	no	>30
Lentigo colour and dimension	dark	dark	black	dark	n.app.	n.app.	n.app.	n.app.	n.app.	n.app.	n.app.	black
Skeletal anomalies	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Short/webbed neck	yes	yes	no	no	yes	no	yes	yes	yes	yes	no	no
Cubitus valgus	no	yes	yes	yes	no	no	no	no	yes	yes	no	no
Broad chest/telethelia	yes	yes	no	yes	no	yes	yes	yes	yes	yes	yes	yes

Absent/hypoplastic eyebrows	no	yes	yes	yes	no	yes	no	yes	yes	yes	yes
Curly hairs	yes	no	yes	yes	yes	yes	yes	no	yes	no	yes
Sparse hair	no	no	yes	yes	yes	no	no	yes	no	yes	no
Hyperkeratosis	no	yes	no	yes	no	no	no	yes	yes	no	no
Keratosis pilaris	yes	yes	no	n.a.	no	n.a.	no	no	n.a.	yes	yes
Hyperhidrosis	yes	yes	yes	n.a.	yes	n.a.	yes	no	n.a.	yes	n.a.
Deep palmar/plantar creases	no	no	no	n.a.	yes	yes	yes	no	yes	yes	no
Dark skin pigmentation	no	yes	no	no	no	no	yes	no	no	yes	no
Naevi (number)	yes	yes	no	no	no	yes	yes	no	no	no	no
Café au lait spots	yes	yes	no	no	no	1	no	no	no	no	no
Lentigo (number)	>100	no	6	no	>10	no	20	no	no	no	>100
Lentigo colour and dimension	brown	n.app.	black	n.app.	black	n.app.	brown	n.app.	n.app.	n.app.	dark
Skeletal anomalies	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Short/webbed neck	yes	yes	no	yes	yes	yes	no	yes	no	yes	no
Cubitus valgus	yes	no	no	no	yes	no	yes	yes	no	yes	yes
Broad chest/telethelia	yes	yes	yes	yes	yes	no	yes	yes	no	yes	no
Pectus excavatum/carinatum	yes	yes	yes	no	no	yes	yes	no	yes	yes	yes
Small joint hyperextensibility	No	yes	no	n.a.	no	yes	yes	yes	n.a.	no	no
Scoliosis	No	no	no	no	yes	no	yes	no	yes	yes	no
Neurologic	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Mental retardation	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no
Seizures	yes	no	no	yes	yes	yes	yes	yes	yes	yes	no
Hypotonia	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	no
Hearing loss	No	no	no	yes	yes	no	no	n.a.	no	no	yes
Coagulation disorders	No	no	no	no	no	no	no	no	no	no	no
Ocular anomalies	S, N	no	yes	CB	CB, N	N	N	N	S	S	S, My
Other features	AP	UT, AN		M, B, SS		AP, AS, FC, SS, DN	UT, H		B, IH, JC	M, DP, VD, CF	M