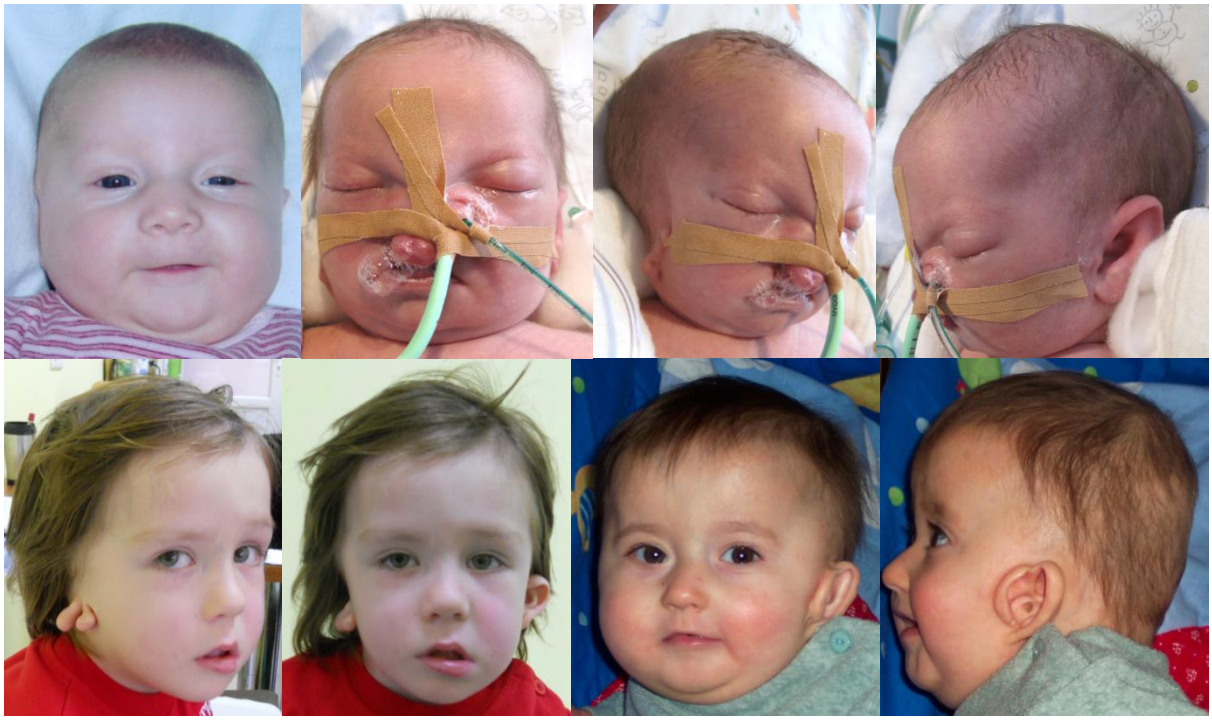
Supplemental Material

Oto-facial syndrome and esophageal atresia, intellectual disability and zygomatic anomalies - expanding the phenotypes associated with *EFTUD2* mutations

Supplementary Figure 1:

Craniofacial phenotype of patients without *EFTUD2* mutation. A. Patient 13 with mild right-sided hemifacial microsomia. B-D- Patient 17 with bilateral cleft lip/palate, right-sided microtia and left-sided preauricular tags. E, F. Patient 21 with right-sided hemifacial microsomia and microtia at both sides. G, H. Patient 15 with left-sided hemifacial microsomia and left-sided mirrow-ear.



Supplementary Table 1: All reported *EFTUD2* mutations organized to their location within the gene and the associated clinical findings

	Patient / Case [ref]	nucleotide position	amino acid substitution	microcephaly	short stature	ID	thumb anomaly	esophageal atresia	CHD
1	Patient 8 [this report]	c.253-1G>A	splice	+	-	Mild	-	+	-
2	Patient 2 [9]	c.351-1G>T	splice	+	+	mod. to severe	-	-	+
3	Patient 6 [this report]	c.594T>G	p.Tyr198*	+	-	moderate	-	+	+
4	Case 6 [3]	c.619+1G>A	splice	+	-	+	-	+	-
5	Case 7 [3]	c.623A>G	p.His208Arg	+	-	++	-	+	-
6	Case 10 [3]	c.670G>A	p.Gly224Arg	+	-	++	-	-	-
7	Patient 7 [15]	c.698del	p.Glu233Gly*fs**3	+	n.r.	+	-	-	+
8	Patient 2 [5]	c.784C>T	p.Arg262Trp	+	-	mild to moderate	-	-	+
9	Patient 6 [5]	c.784_787deldup788_799TGATCCTGGAGC	p.Arg262*fs**1	+	+	+	+	-	+
10	Patient 1 [15]	c.994+5G>A	splice	+	n.r.	+	+	+	-
11	Patient 1-3 [this report]	c.994+1G>C	splice	+/+/-	-/+/-	mild/severe/-	-/-/-	+/+/-	+/+/-
12	Case 12 [3]	c.1058+3_1058+7del	?	-	-	-	+	+	+
13	Patient 7 [5]	c.1172_1179delGCCTCCCA	p.Ser391Thr*fs**57	+	-	moderate	-	-	+
14	Patient 3 [9]	c.1306C>G	p.Gln436Glu	+	+	Mild	+	-	-
15	Patient 12 [5]	c.1426T>C	p.Cys476Arg	+	-	moderate	+	-	-
16	Patient 10 [5]	c.1607+3A>G	p.Tyr537*fs**25	+	-	mild to moderate	n.r.	-	+
17	Case 5 [3]	c.1705C>T	p.Arg569*	+	-	+	-	+	-
18	Patient 4 [5]	c.1758_1759delTG	p.Ser586Ser*fs**19	+	-	mod. to severe	n.r.	-	-
19	Patient 11 [5]	c.1910T>C	p.Leu637Arg	+	+	mild to moderate	-	-	-
20	Patient 8 [5]	c.2155C>T	p.Gln719*	+	-	moderate	-	-	-
21	Case 8 [3]	c.2198G>A	p.Trp733*	+	-	++	-	-	+
22	Case 3 [3]	c.2259+1G>A	splice	+	+	++	-	+	+
23	Case 9 [3]	c.2347+66A>G	?	-	-	+	-	+	+
24	Patient 1 [9]	c.2485G>A	p.Glu829Lys	-	-	Mild	+	-	-
25	Patient 9 [5]	c.2493C>A	p.Tyr831*	+	-	severe	+	-	+
26	Patient [8]	c.2495C>G	p.Tyr832*	+	n.r.	n.r.	+	-	n.r.
27	Patient 7 [this report]	c.2562-1G>C	splice	+	-	moderate	+	-	-
28	Case 4 [3]	c.2619_2621delinsGGTC	p.Phe874Valfs*11	+	-	++	+	-	-
29	Patient 4,5 [this report]	c.2622dupT	p.Ile875Tyr*fs**10	+/n.r.	-/n.r.	mild/mild	-/-	+/-	n.r./n.r.
30	Patient 3 [5]	c.2770C>T	p.Glu924*	+	-	Mild	+	-	-
31	Case 11 [3]	c.2823+1del	splice	n.r./+	n.r./-	n.r./+	-/-	+/-	-/-
32	Patient 5 [5]	deletion of 10 genes, including *EFTUD2*		+	-	moderate to severe	n.r.	-	+
33	Case 1 [3]	deletion of 4 genes, including *EFTUD2*		-	-	++	-	+	-
34	Case 2 [3]	deletion of 4 genes, including *EFTUD2*		+	n.r.	++	-	+	+
35	Patient 1 [5]	deletion of the last 9 exons of *EFTUD2*		+	-	+	+	-	-
				32/37	6/33	2/37	12/36	15/39	16/36

We changed the mutations from Luquetti et al. according to the described genomic position.

Supplementary Table 2: Clinical data of 14 patients tested negative for *EFTUD2* mutations

	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18	Patient 19	Patient 20	Patient 21	Patient 22
Sex	m	m	m	m	f	m	f	m	f	m	m	m	m	f
Consanguinity	-	-	-	-	-	-	-	-	-	-	n.r.	-	n.r.	-
Development								-	-					
ID	+	- (IQ 99)	+	+	+	-	n.r.	n.r.	n.r.	+	+	+ (sitting with 14 mo.)	+	Mild delay
Age at walking [mo]	13	14	21	n.r.	16	n.r.	n.r.	n.r.	n.r.	15	15	n.r.	12	18
Age at first words [mo]	13	6 - 7	36	n.r.	11	n.r.	n.r.	n.r.	n.r.	24	10	n.r.	9	22
Epilepsy	-	seizures after surgery	-	febrile seizures	-	-	-	-	-	-	+	-	-	-
Pregnancy												ICSI; twin died in 4th wk.		Early rupture of membranes (30w)
Polyhydramnios	-	+	- (oligohydr.)	-	-	-	-	+	+	n.r.	n.r.	-	-	+
Measurements														
Gestational weeks at birth	38	38	32	35	39	40	37	40	37	40	n.r.	42	38	33
Weight/SD	3090/-0.50	2250/-2.43	700/-3.04	1960/-1.50	3340/0.00	3330/-0.67	2390/-1.34	3115/-1.15	2240/-1.69	2400/-2.78	n.r.	3360/-0.94	3100/-0.48	1640/-0.8
Length/SD	51/-0.04	47/-1.78	32/-3.61	40/-2.89	48/-1.40	51/-0.65	46/-1.46	52/-0.22	45/-1.88	49/-1.52	n.r.	52/-0.58	51/-0.04	n.r.
OFC/SD	33/-1.36	33.5/-1.00	23.6/-3.58	30/-1.94	33.5/-0.85	36.5/-0.69	32/-1.35	n.r.	32/-1.36	34/-1.23	n.r.	35/-0.79	n.r.	28.3/-1.3
Age at examination [y]	12 $^{10}/_{12}$	5 $^{6}/_{12}$	6	2 $^{1}/_{12}$	2 $^{1}/_{12}$	0 $^{9}/_{12}$	0 $^{6}/_{12}$	n.r.	0 $^{1}/_{12}$	5 $^{6}/_{12}$	3 $^{3}/_{12}$	1 $^{2}/_{12}$	3 $^{5}/_{12}$	4y
Height/SD	140/-1.98	102/-3.16	107/-2.13	85/-0.78	84/-1.06	72/-0.21	64/-1.01	n.r.	50/-1.74	108/-1.92	101/1.04	80/1.60	95/-0.55	88/-4.0
Weight/BMI	28/14.29	13.8/13.26	16.5/14.41	9/12.46	12/17.01	9.3/17.04	5.7/13.92	n.r.	3/12	17/14.57	16/15.68	9.8/15.31	15/16.62	11.5/14.8
OFC/SD	48/-4.12	49.5/-2.07	46.7/-4.15	44/-4.00	45/-2.60	46/0.16	39/3.45	n.r.	n.r.	49/-2.44	48/-2.05	45/-1.65	52/0.87	44.5/-4.4
Craniofacial dysmorphism														
Facial asymmetry	-	+	-	-	+	+	+	+	+	+ (anophth. on the left)	+	+	+	-
Hyperplastic supraorbital ridges	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Frontal bossing	-	-	-	+	-	+	+	-	+	-	-	-	-	+
Upslanting palpebral fissures	+	+	-	-	-	-	-	-	- (downsl.)	-	-	+	-	-
Epibulbar	-	-	-	-	-	-	-	-	-	-	-	-	-	-

dermoid														
Microtia/with squared earlobe	-	+/+	-	-	-	+/-	+/-	+/-	+/-	-	-	+/-	+/-	+
Preauricular tag	-	-	-	-	-	-	+	+	-	+	+	+	-	-
Preauricular pit	-	-	-	-	-	-	-	-	-	-	-	-	+	-
A-/hypoplasia of external ear canal	-	-	-	-	-	-	-	n.r.	+	-	n.r.	+	n.r.	+
Hearing loss	-	+ (cond.)	-	-	-	+	n.r.	n.r.	n.r.	-	n.r.	n.r.		+
Cleft Palate	-	+ (median)	-	-	-	-	+	+ (bilateral)	-	-	+	+ (soft palate)	-	-
Reduced mouth opening	+	-	-	-	-	-	-	n.r.	+	-	n.r.	-	n.r.	-
Micrognathia	+	+	+	+	+	+	+	+	+	-	-	+	-	+
Malformations														
Tracheostomy	-	-	-	-	-	-	-	-	+	-	-	-	-	-
Esophageal atresia	-	-	-	-	-	-	-	+	+ (and esophageal-trachel fistula)	-	-	-	-	+
CHD	-	+ (DORV)	-	+ (VSD, PFO)	+ (pulm. stenosis)	+ (PFO)	-	+ (small VSD)	+ (PDA, VSD, dextropositio)	-	n.r.	+ (VSD, PDA)	-	-
Scoliosis	+ (and rigid spine)	-	-	-	-	-	vertebral deformity	n.r.	n.r.	-	-	+ (and Sprengel deformity)	-	-
Cleft of zygomatic bone	-	-	-	-	-	-	-	-	-	-	n.r.	-	-	n.r.
Choanal atresia	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inner/middle ear malformations	-	n.r.	-	n.r.	n.r.	-	n.r.	n.r.	n.r.	-	n.r.	n.r.	n.r.	n.r.
Anomalies of hands		edema (after birth)						edema (after birth)						
Proximally placed/duplicated thumbs	-	-	hypoplastic thumbs	-	-	-	-	-	-	-	-	-	-	-
Clinodactyly V	+	-	-	-	-	-	-	-	-	-	-	-	-	-