DELETION OF *ERF* AND *CIC* CAUSES ABNORMAL SKULL MORPHOLOGY AND GLOBAL DEVELOPMENTAL DELAY

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Running Title: *ERF* and *CIC* deletion and abnormal skull morphology

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SUPPLEMENTAL MATERIAL:

Supplemental Table S1. Previously reported *ERF* variants implicated in variable craniosynostosis.

Nucleotide change	Protein change	Craniosynostosis type / Phenotype	Population frequency (gnomAD)	Reference
c.1A>T	p.Met1?	P + OHT, mild exorbitism, malar hypoplasia, broad thumbs/first toes, early CM (1 pt)	absent	Glass (2019) PMID: 30758909
c.1A>G	p.Met1?	MS + proptosis, hypertelorism, malar hypoplasia, depressed nasal bridge, ectopic posterior pituitary, CM (1 pt)	absent	Chaudhry (2015) PMID: 26097063
c.3G>A	p.Met1?	MS (4 pts, 1 family)	absent	Twigg (2013) PMID: 23354439
c.21A>T	p.(Thr7=)	SS (3 pts, 1 family)	absent	Twigg (2013) PMID: 23354439
c.23-2A>G	-	BI-ME + proptosis, hypertelorism, depressed nasal bridge, speech delay (1 pt)	absent	Chaudhry (2015) PMID: 26097063
c.90_99del	p.Trp30Cysfs*44	SS + developmental delay (1 pt)	absent	Lee (2018) PMID: 29215649
c.157G>A	p.Gly53Arg	SS + OHT, exorbitism, malar hypoplasia, low-set ears, open mouth appearance (1 pt)	absent	Glass (2019) PMID: 30758909
c.161A>G	p.Glu54Gly	UL + medial epicanthic folds, short upturned nose (1 pt); CC-SS, OHT, exorbitism (1 pt, same family)	absent	Glass (2019) PMID: 30758909
c.194G>A	p.Arg65Gln	SS (2 pts, 1 family); BI (1 pt)	absent	Twigg (2013) PMID: 23354439; Lee (2018) PMID: 29215649
c.202G>C	p.Gly68Arg	SS-UL + hydrocephalus, macrocephaly, dysplastic auricles (1 pt); ME + dysplastic auricles (1 pt, same family); SS (1 pt, same family)	absent	Glass (2019) PMID: 30758909
c.247C>T	p.Arg83Trp	CC variable (10 pts, 1 family, with reduced penetrance in 4 pts); SB + OHT, exorbitism (1 pt, different family)	absent	Glass (2019) PMID: 30758909
c.248G>A	p.Arg83Gln	CC variable + OHT, exorbitism, malar hypoplasia, medial epicanthic folds, CM (2 pts, 1 family)	1/250822 =0.0004%	Glass (2019) PMID: 30758909
c.256C>T	p.Arg86Cys	MS (1 pt)	absent	Twigg (2013) PMID: 23354439
c.257G>A	p.Arg86His	SB + hypertelorism, vertical nasal displacement (2 pts, 1 family)	1/250504 =0.0004%	Yoon (2019) PMID: 31754721

c.301C>T	p.Arg101Trp	P + OHT, exorbitism, malar hypoplasia, early CM (3 pts, 1 family, with reduced penetrance in other 2 pts)	1/251472 =0.0004%	Glass (2019) PMID: 30758909
c.311A>G	p.Tyr104Cys	Multiple congenital anomalies	1/251472 =0.0004%	Retterer (2016) PMID: 26633542
c.373+1G>C	-	Crouzon syndrome	absent	Lee (2018) PMID: 29215649
c.383T>G	p.Val128Gly	UC + low anterior hairline, asymmetric face, flat malar regions, low-set and posteriorly rotated right ear, normal development (1 pt)	7/241336 =0.0029%	Topa (2020) PMID: 31837199
c.547C>T	p.Arg183*	MS (4 pts, 1 family); SS + OHT, mild exorbitism, malar hypoplasia (1 pt, different family); SB + OHT, mild exorbitism, malar hypoplasia, short lateral metatarsals (3 pts, 1 family, with reduced penetrance in 1 pt)	absent	Twigg (2013) PMID: 23354439; Glass (2019) PMID: 30758909
c.652C>T	p.Arg218*	SB + OHT, mild exorbitism (2 pts, 1 family, reduced penetrance in other pt)	0%	Glass (2019) PMID: 30758909
c.886G>A	p.Gly296Ser	SS, hypertelorism, vertical nasal displacement (1pt)	5/245366 =0.002%; 1 homozygous	Yoon (2019) PMID: 31754721
c.891_892del	p.Gly299Argfs*9	P (1 pt); M (4 pts, 2 families); B-UL + OHT, exorbitism, malar hypoplasia, early CM (1pt)	absent	Twigg (2013) PMID: 23354439; Glass (2019) PMID: 30758909
c.985_1027del	p.Arg329Serfs*54	SS, hypertelorism, frontal bossing, sunken midface, short stature (2 pts, 1 family)	absent	Yoon (2019) PMID: 31754721
c.1103C>T	p.Ser368Phe	UC (1 pt who also carries *POR* p.Arg453His)	absent	Clarke (2018) PMID: 29168297
c.1201_1202del	p.Lys401Glufs*10	P (1 pt); P + OHT, malar hypoplasia, CM, frontal bossing, long philtrum, high arched palate, low-set ears, inverted nipples, bilateral 5th finger clinodactyly, broad DP of halluces, sacral dimple (1 pt, different family); UC + long philtrum, short up-turned nose, joint hypermobility (2 pts, 1 family, with reduced penetrance in other pt); BLSS and SS.	1/236032 =0.0004%	Twigg (2013) PMID: 23354439; Glass (2019) PMID: 30758909; Korberg (2020) PMID: 32370745
c.1214G>A	p.Ser405Asn	ME (1 pt)	absent	Yoon (2019) PMID: 31754721

c.1270C>T	p.Gln424*	P (3 pts, 1 family); SB + OHT (1 pt, different family)	absent	Twigg (2013) PMID: 23354439; Glass (2019) PMID: 30758909
c.1300G>A	p.Glu434Lys	UC + high forehead, tendency toward turricephaly preoperative, prominent scalp veins, shallow orbits, mild right proptosis, flat malar regions, small mouth, hypotelorism, asymmetric facial midline, right epicanthus, flat malar regions, midface hypoplasia, low-set and anteriorly rotated ears and cup-shaped right helix, psychomotor delay, strabismus, tapering fingers, mild skin syndactyly of fingers, short proximal phalanges 2-5, bilateral syndactyly 2nd-3rd toes, overlapping 2nd and 4th toes right foot, clinodactyly 3rd toe, diarrhea, gastroesophageal reflux, food allergy, growth delay, short stature, sparse hair (1 pt)	3/245440 =0.0012%	Topa (2020) PMID: 31837199
c.1390_1391dup	p.Lys465Leufs*67	P + OHT, exorbitism, malar hypoplasia, left proximal radio-ulnar synostosis, C5/6 vertebral fusion, broad thumbs (1pt); SS + OHT, exorbitism (1 pt, same family)	absent	Glass (2019) PMID: 30758909
c.1512del	p.Phe504Leufs*27	CC (1 pt)	absent	Twigg (2013) PMID: 23354439
c.1593_1594insCAGA	p.Ser532Glnfs*3	ME (3 pts, 1 fam)	absent	Timberlake (2017) PMID: 28808027

BI: bicoronal; BLSS: bilateral lambdoid and sagittal synostosis; CC: complex craniosynostosis; CM: Chiari-1 malformation; ME: metopic; MS: multiple-suture synostosis; OHT: orbital hypertelorism; P: pansynostosis; pt(s): patient(s); SB: Sagittal bilambdoid; SS: sagittal synostosis; UC: unicoronal; UL: unilambdoid. All variants described for *ERF* (NM_006494.3) in HGMD® Professional 2021.1 with the exception of c.266A>G, c.288G>T and c.1460G>A associated with distinct phenotypes; variants frequencies from https://gnomad.broadinstitute.org/.

Supplemental Table S2. Previously reported *CIC* sequence variants implicated in neurodevelopmental phenotypes (mostly *de novo*).

Nucleotide change	Protein change	Phenotype	Population frequency (gnomAD)	Reference
c.457C>T	p.Leu153Phe	ASD (1/2,508 pts)	absent	Iossifov (2014) PMID: 25363768
c.673C>T	p.Gln225*	ASD + CLP (1/2,620 pts)	absent	Yuen (2017) PMID: 28263302
c.680A>G	p.Asn227Ser	nsID (1/236 pts)	absent	Athanasakis (2014) PMID: 24307393
c.791A>G	p.His264Arg	Schizophrenia (1/623 pts)	absent	Fromer (2014) PMID: 24463507
c.820C>T	p.Arg274*	ASD (1/2,508 pts)	1/246948 =0.0004%	Iossifov (2014) PMID: 25363768; PMID: 28191890 uses same data set
c.1057C>T	p.Arg353*	DD, ID, ASD, seizures, macrocephaly, abnormal MRI, mild telangiectasia (1 pt)	absent	Lu (2017) PMID: 28288114
c.1474C>T	p.Arg492Trp	nsID (1/10 pts)	1/250214 =0.0004%	Vissers (2010) PMID: 21076407
c.1801_1808 dup	p.Glu604Argfs*127	DD, ID, seizures (2 siblings) + pulmonary stenosis (sib A) + heart murmur, mild telangiectasia (sib B)	absent	Lu (2017) PMID: 28288114
c.1927G>C	p.Gly643Arg	ASD, DD (3 affected siblings, variable severity)	absent	Mahfouz (2020) PMID: 32382396
c.2571_2578 delinsC	p.Thr859Alafs*63	DD, ID, ASD, abnormal MRI, mild hypotonia (1 pt)	absent	Lu (2017) PMID: 28288114
c.2974C>T	p.Gln992*	DD, ID, ASD, ADHD, abnormal MRI, marfanoid habitus, stereotypic movements (1 pt)	absent	Lu (2017) PMID: 28288114
c.3795+1G>C	-	nsID (1/108 pts)	absent	Kim (2019) PMID: 30952489

ASD: autism spectrum disorder; CLP: cleft lip and palate; DD: developmental delay; ID: intellectual disability; MRI: magnetic resonance imaging; nsID: nonsyndromic intellectual disability; pt(s): patient(s). All variants described for *CIC* (NM_015125.4) in HGMD® Professional 2021.1; variants frequencies from https://gnomad.broadinstitute.org/.