IRIS AperTO

UNIVERSITÀ DEGLI STUDI DI TORINO

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

A fetal case of microphthalmia and limb anomalies with abnormal neuronal migration associated with SMOC1 biallelic variants

This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1702761 since 2019-11-19T14:52:06Z

Published version:

DOI:10.1016/j.ejmg.2018.11.012

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

06 October 2026

A fetal case of microphthalmia and limb anomalies with abnormal neuronal migration associated with *SMOC1* biallelic variants.

Cecilia Mancini [1*], Andrea Zonta [2*], Giovanni Botta [3], Andrea Breda Klobus [4], Stefano Valbonesi [4], Barbara Pasini [2], Elisa Giorgio [1], Elsa Viora [5], Alfredo Brusco [1, 2], Alessandro Brussino [1].

*These authors equally contributed to the work.

[1] University of Torino, Department of Medical Sciences, 10126, Torino, Italy.

[2] Città della Salute e della Scienza University Hospital, Medical Genetics Unit, 10126, Torino, Italy.

[3] Città della Salute e della Scienza University Hospital, Departments of Pathology, 10126, Torino, Italy.

[4] Breda Genetics, Brescia, Italy

[5] Città della Salute e della Scienza University Hospital, Department of Gynecology and Obstetrics, Ultrasound and Prenatal diagnosis Unit, 10126, Torino, Italy.

Corresponding author: Alfredo Brusco, University of Torino, Department of Medical Sciences, via Santena 19, 10126, Torino, Italy. Fax +390112365926; e-mail: alfredo.brusco@unito.it.

Short title: Two novel *SMOC1* mutations

Keywords: SMOC1;Microphthalmia with limb anomalies; Waardenburg anophthalmia syndrome; ophthalmo-acromelic syndrome; abnormal neuronal migration

Conflict of interest: Drs Andrea Breda Klobus and Stefano Valbonesi are employees of the company "Breda Genetics srl" involved in genetic testing.

Abstract (350 words)

Microphthalmia with limb anomalies (MLA, OMIM 206920) is a rare autosomal-recessive disease caused by recessive mutations in the *SMOC1* gene. It is characterized by ocular disorders (microphtalmia or anophtalmia) and limb anomalies (oligodactyly, syndactyly, and synostosis of the 4^{th} and 5^{th} metacarpals), variably associated with long bone hypoplasia, horseshoe kidney, venous anomalies, vertebral anomalies, developmental delay, and intellectual disability.

Here, we report the case of a woman who interrupted her pregnancy after ultrasound scans revealed a depression of the frontal bone, posterior fossa anomalies, cerebral ventricular enlargement, cleft spine involving the sacral and lower-lumbar vertebrae, and bilateral microphthalmia. Micrognathia, four fingers in both feet and a slight tibial bowing were added to the clinical picture after fetal autopsy. Exome sequencing identified two mutations in the *SMOC1* gene, each inherited from one of the parents: c.709G>T - p.(Glu237*) on exon 8 and c.1223G>A - p.(Cys408Tyr) on exon 11, both predicted to be pathogenic by different bioinformatics software. Brain histopathology showed an abnormal cortical neuronal migration, which could be related to the SMOC1 protein function, given its role in cellular signaling, proliferation and migration. Finally, we summarize phenotypic and genetic data of known MLA cases showing that our case has some unique features (Chiari II malformation; focal neuropathological alterations) that could be part of the variable phenotype of SMOC1-associated diseases.

Introduction

Microphthalmia with limb anomalies (MLA, OMIM 206920), also known as Waardenburg anophthalmia syndrome or ophthalmo-acromelic syndrome, is a rare autosomal-recessive disease with less than 40 cases reported in the literature [1-4]. MLA is clinically characterized by ocular anomalies (microphtalmia or anophtalmia), and limb anomalies, such as oligodactyly, syndactyly, and synostosis of the 4^{th} and 5^{th} metacarpals [5-7]. Other reported malformations include long bone hypoplasia, horseshoe kidney, and venous or vertebral anomalies [3]. Developmental delays and intellectual disability may also be present [8].

The syndrome is caused by recessive mutations in the secreted protein acidic and rich in cysteine-related modular calcium binding 1 gene (*SMOC1,* OMIM 608488) on chromosome 14q24 [2]. This gene belongs to the SMOC family, a group of extracellular glycoproteins widely expressed in various tissues that localize to basement membranes. In mice, *Smoc1* is highly expressed in the developing eye and limb: a *Smoc1* null mouse model showed delayed growth, with defects in the eyes and optic nerves, and a peculiar hindlimb phenotype characterized by syndactyly and pes valgus, bowed tibiae, and hypoplastic fibulae, strongly recapitulating eyes and limb anomalies of MLA patients [2].

Here, we describe an Italian family with two fetuses affected by Waardenburg anophtalmia syndrome and identify two novel variants in the *SMOC1* gene.

Clinical report.

A woman (III-3, Fig.1A) was brought to medical attention at 17 weeks and 3 days gestation, following a maternal serum prenatal screening that revealed elevated alpha-fetoprotein levels (AFP = 162 U/mL), corresponding to 5.25 multiple of median (MoM), thus suggesting a possible neural tube defect. Fetal ultrasound (US) showed a depression of the frontal bone (lemon sign), and an abnormal positioning of the cerebellum around the brain stem coupled with the downward-sliding of the posterior fossa contents (banana sign), cerebral ventricular enlargement, cleft spine involving the sacral and lower-lumbar vertebrae, and bilateral microphthalmia. Following the US results and

psychological counseling, the parents decided to interrupt the pregnancy at 18 weeks (IV.2, Fig.1A), and gave consent for a histopathological exam. QF-PCR on amniotic fluid did not reveal numerical anomalies of chromosomes 13, 18, and 21. Fetal karyotype was 46,XY.

Anamnestic data revealed that a previous pregnancy (IV.1, Fig.1A) was interrupted at 13 weeks after prenatal US scans showed bilateral lower limb hypoplasia and malpositioned feet. No further analyses were performed on this fetus.

Informed consent was obtained from the parents of the index case and the internal Ethics Committee of the Department of Medical Sciences, University of Torino, Italy approved the study.

Fetal DNA was sent to an external company (Breda Genetics, Brescia, Italy) to perform exome-sequencing analysis using the Human All Exon V6 kit on a NextSeq500 platform (Agilent technologies, Santa Clara, CA, USA). Exome sequencing revealed two variants in the *SMOC1* gene (ref NM_022137.5; GenBank protein AAH11548); c.709G>T - p.(Glu237*) on exon 8 and c.1223G>A - p.(Cys408Tyr) on exon 11 (Fig.1B)(ClinVar SCV000809038, SCV000809039; http://www.ncbi.nlm.nih.gov/clinvar). Sequencing of *SMOC1* in both parents revealed that the mother carried the c.709G>T variant and the father carried the c.1223G>A variant.

As parents gave consent to determine the exome sequencing secondary findings, a c.660ins18 - p.(Pro220insAspCysLysAspLysSer) variant in exon 4 of the low density lipoprotein receptor gene (*LDLR*, NM_000527) was reported. However, it was not possible to test the segregation of this variant in the father or the paternal relatives.

Fetal autopsy, histopathological examination and exome sequencing.

Fetal autopsy showed a globally small fetus with male external genitalia, weighing 166 g. Crown-rump length (CRL) was 12 cm, crown-heel length (CHL) was 20 cm, foot length was 2 cm, biparietal diameter (BPD) was 4 cm, and occipito-frontal diameter was 4.5 cm. Externally, it showed micrognathia, arachnodactyly of the hands, cleft spine with a 0.15 cm sacral meningocele, and four fingers in both feet (Fig.1C). X-ray scan revealed a slight tibial bowing (Fig1.C). Brain, thoracic and

abdominal organs were normal, but the histopathological exam showed a focal abnormal cortical neuronal migration (Fig.1D).

Discussion.

We report the case of a woman who decided to interrupt her pregnancy after the ultrasound finding of multiple congenital anomalies. Autopsy data suggested MLA syndrome, a diagnosis corroborated by bioinformatics analysis with the Phenomizer tool [9]; selecting lower limb defects as mandatory (since they were visible in both pregnancies), MLA syndrome was among the more probable diseases, scoring a p-value of 0.08. Indeed, exome sequencing analysis showed two heterozygous variants in the *SMOC1* gene. Neither variant was reported in the literature. The c.709G>T creates a stop codon, is predicted to encode for a truncated, non-functional protein, and is not present in the gnomAD database (http://gnomad.broadinstitute.org). The c.1223G>A is a missense variant affecting a highly conserved cysteine residue. A single occurrence of this variant is reported in the gnomAD database with a frequency = $4x10^{-6}$ (rs1326644602). Bioinformatics analysis using Varsome (https://varsome.com/) labeled this variant being of uncertain significance using the American College of Medical Genetics and Genomics classification [10]; however, combining the results of different bioinformatics tools, yielded a DANN score, which classifies the pathogenicity of genetic variants between 0 (less damaging) and 1 (most damaging), of 0.998 [11]. To verify if the two variants were *in cis* or *in trans* on the *SMOC1* gene, we tested both parents; each resulted to be the carrier of one of the two mutations, demonstrating the fetus had a compound heterozygous genotype. Although most of the mutations associated with MLA reported so far are nonsense or affect a splice site (Fig.1E, highlighted in red and blue, respectively), three different missense variants segregating with the disease have been published, namely the c.812G>A - p.(Cys271Tyr) [1], and the c.833C>T - p.(Arg278Cys) and c.848C>A - p.(Thr283Asn) [3]. Taken together, these data indicate that the fetus was affected by MLA syndrome associated with two novel compound heterozygous mutations in the *SMOC1* gene. Interestingly, a previous pregnancy of the mother was interrupted after prenatal US

revealed the presence of lower limb anomalies: although no further physical, histological or genetic tests were performed at the time, the lower limb involvement may suggest that this fetus was also affected by the MLA syndrome.

To date, 22 MLA patients from 14 families have been reported to carry mutations in the *SMOC1* gene [1-4, 12] (see table 1 for a comparison of published clinical and genetic data)(Fig. 1E). Geographical origin of patients varies. Most pathogenic variants are nonsense (stop codon gain and single base frameshifts); a few were splicing mutations that probably induced skipping of the nearby exons, which is predicted to lead to an out-of-frame transcript. Among these, we included the c.857G>A variant [12], which affects the last base of exon 8; this variant was predicted to change the amino acid, and it is likely to cause the skipping of exon 8.

Only three known variants are missense, all located in exon 8 which encodes for most of the second thyroglobulin domain. The fourth missense change was found in our patient, and is located in exon 11, likely affecting the Ca^{++} extracellular binding domain.

The case we have described here is the first fetal diagnosis. In addition to MLA, cleft spine and sliding of the posterior fossa content (Chiari II malformation) were visible, never prevbiously reported in MLA. However, given the high incidence of Chiari II malformation at birth (~1:1,000) [13], we cannot exclude this is a coincidental finding.

As MLA is a rare recessive disease, consanguinity between parents of an affected subject is often reported. Indeed, all published MLA patients carry a homozygous *SMOC1* pathogenic variant. This suggests that, even when there is no reported consanguinity, parents may have inherited the mutation from a common ancestor. Our proband has the only occurrence of compound heterozygosity for *SMOC1* variants.

Finally, we had the unprecedented opportunity to perform a brain histopathological exam, showing an alteration of neuronal migration. SMOC1, as well as other proteins of the extracellular matrix is known to play a role in cell signaling, proliferation, and migration [14], although its function has never been linked to the central nervous system development. The clinical consequences of altered

neuronal migration are still not completely understood, but it is intriguing that eight MLA patients present intellectual disability and one case has epilepsy, which is known to be associated with focal cortical alterations [15]. Other brain histopathological exams from MLA-affected subjects are needed to further investigate if this focal altered neuronal migration is part of the array of signs and symptoms of MLA.

In addition to *SMOC1* variants, whole exome sequencing identified an insertion in exon 4 of the *LDLR* gene as an incidental finding. In the father of the fetus and multiple members of his family, a history of hypercholesterolemia was known (Fig. 1A). Exon 4 of the *LDLR* gene is frequently hit by mutations associated with hypercholesterolemia [16], and a similar variant (c.664_681dup18, p.Asp227_Glu228insCysLysAspLysSerAsp) was reported as probably pathogenic [17]. As it was not possible to verify the presence of this variant in other family members, we can only speculate that this was the cause of the familial hypercholesterolemia reported in the father and his relatives.

In conclusion, we have further shown the diagnostic value of exome sequencing in solving complex cases and describe two novel variants in the *SMOC1* gene associated with a unique feature (Chiari II malformation), and focal neuropathological alterations that may be characteristic of MLA.

Acknowledgements

Authors are indebted the family for taking part into the study. This work was supported by: MURST-ex60% to AB. CM and EG were supported by Fondazione Veronesi fellowship 2017-2018. This research received funding specifically appointed to Department of Medical Sciences from the Italian Ministry for Education, University and Research (Ministero dell'Istruzione, dell'Università e della Ricerca - MIUR) under the programme "Dipartimenti di Eccellenza 2018 – 2022", Project code D15D18000410001.

Figure 1. Pedigree, gene-protein scheme, X-ray, and brain histopathology.

Panel A. Pedigree of the reported family. Squares represent male subjects, circles represent female subjects, and black triangles indicate a termination of pregnancy (VTP = voluntary termination of pregnancy, TTP = therapeutic termination of pregnancy). A solid black wedge indicates subjects affected by hypercholesterolemia. Subjects whose DNA was available are marked with a bar above the symbol; below, the variants identified are reported. Panel B shows electropherograms of the two mutations identified in the *SMOC1* gene in III-2. In panel C, frontal (left) and lateral (right) X-ray analysis of the fetus showing: 1- Micrognathia; 2- Arachnodactyly of the hands; 3- Cleft spine; 4- Bowed tibiae; 5- Foot oligodactyly. Panel D shows two hematoxylin/eosin-stained sections of the brain parietal cortex. The upper panel (control) displays a physiological pattern of neuronal migration. The lower panel (III-2) shows a focal alteration of neuronal migration. Panel E shows a scheme of the *SMOC1* gene and its protein (above), with the main protein domains (amino acids interval in brackets) (https://www.ebi.ac.uk/interpro/). The 12 *SMOC1* exons are represented in scale. Below known reported variants (see Table 1 for clinical details) with the protein change or the predicted effect on splicing. Only four variants, including the c.1223G>A, are missense changes (purple). The two variants described in the manuscript are boxed. Nomenclature of some published mutations has been edited to adhere to the sequencing data and nucleotide/amino acid position (see ClinVar).

References

[1] A. Ullah, M. Umair, F. Ahmad, D. Muhammad, S. Basit, W. Ahmad, A novel homozygous variant in the SMOC1 gene underlying Waardenburg anophthalmia syndrome, Ophthalmic Genet, 38 (2017) 335-339.

[2] I. Okada, H. Hamanoue, K. Terada, T. Tohma, A. Megarbane, E. Chouery, J. Abou-Ghoch, N. Jalkh, O. Cogulu, F. Ozkinay, K. Horie, J. Takeda, T. Furuichi, S. Ikegawa, K. Nishiyama, S. Miyatake, A. Nishimura, T. Mizuguchi, N. Niikawa, F. Hirahara, T. Kaname, K. Yoshiura, Y. Tsurusaki, H. Doi, N. Miyake, T. Furukawa, N. Matsumoto, H. Saitsu, SMOC1 is essential for ocular and limb development in humans and mice, Am J Hum Genet, 88 (2011) 30-41.

[3] J. Rainger, E. van Beusekom, J.K. Ramsay, L. McKie, L. Al-Gazali, R. Pallotta, A. Saponari, P. Branney, M. Fisher, H. Morrison, L. Bicknell, P. Gautier, P. Perry, K. Sokhi, D. Sexton, T.M. Bardakjian, A.S. Schneider, N. Elcioglu, F. Ozkinay, R. Koenig, A. Megarbane, C.N. Semerci, A. Khan, S. Zafar, R. Hennekam, S.B. Sousa, L. Ramos, L. Garavelli, A.S. Furga, A. Wischmeijer, I.J. Jackson, G. Gillessen-Kaesbach, H.G. Brunner, D. Wieczorek, H. van Bokhoven, D.R. Fitzpatrick, Loss of the BMP antagonist, SMOC-1, causes Ophthalmo-acromelic (Waardenburg Anophthalmia) syndrome in humans and mice, PLoS Genet, 7 (2011) e1002114.

[4] H. Abouzeid, G. Boisset, T. Favez, M. Youssef, I. Marzouk, N. Shakankiry, N. Bayoumi, P. Descombes, C. Agosti, F.L. Munier, D.F. Schorderet, Mutations in the SPARC-related modular calcium-binding protein 1 gene, SMOC1, cause waardenburg anophthalmia syndrome, Am J Hum Genet, 88 (2011) 92-98.

[5] P.J. Waardenburg, G.H. Jonkers, A specific type of dominant progressive dystrophy of the cornea, developing after birth, Acta Ophthalmol (Copenh), 39 (1961) 919-923.

[6] M.L. Teiber, J.A. Garrido, C.Z. Barreiro, Ophthalmo-acromelic syndrome: report of a case with vertebral anomalies, Am J Med Genet A, 143A (2007) 2460-2462.

[7] L. Garavelli, S. Pedori, R. Dal Zotto, F. Franchi, M. Marinelli, G.F. Croci, S. Bellato, A. Ammenti, R. Virdis, G. Banchini, A. Superti-Furga, Anophthalmos with limb anomalies (Waardenburg opththalmo-acromelic syndrome): report of a new Italian case with renal anomaly and review, Genetic counseling, 17 (2006) 449-455.

[8] Z. Suyugul, M. Seven, S. Hacihanefioglu, A. Kartal, N. Suyugul, A. Cenani, Anophthalmia-Waardenburg syndrome: a report of three cases, Am J Med Genet, 62 (1996) 391-397.

[9] S. Kohler, M.H. Schulz, P. Krawitz, S. Bauer, S. Dolken, C.E. Ott, C. Mundlos, D. Horn, S. Mundlos, P.N. Robinson, Clinical diagnostics in human genetics with semantic similarity searches in ontologies, Am J Hum Genet, 85 (2009) 457-464.

[10] S. Richards, N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W.W. Grody, M. Hegde, E. Lyon, E. Spector, K. Voelkerding, H.L. Rehm, A.L.Q.A. Committee, Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, Genetics in medicine : official journal of the American College of Medical Genetics, 17 (2015) 405-424.
[11] D. Quang, Y. Chen, X. Xie, DANN: a deep learning approach for annotating the pathogenicity of genetic variants, Bioinformatics, 31 (2015) 761-763.
[12] M.A. Aldahmesh, J.Y. Mohamed, H.S. Alkuraya, I.C. Verma, R.D. Puri, A.A. Alaiya, W.B. Rizzo, F.S. Alkuraya, Recessive mutations in ELOVL4 cause ichthyosis, intellectual disability, and spastic quadriplegia, Am J Hum Genet, 89 (2011) 745-750.
[13] K. Furuya, K. Sano, H. Segawa, K. Ide, H. Yoneyama, Symptomatic tonsillar ectopia, J Neurol Neurosurg Psychiatry, 64 (1998) 221-226.
[14] D.E. Pazin, K.H. Albrecht, Developmental expression of Smoc1 and Smoc2 suggests potential roles in fetal gonad and reproductive tract differentiation, Dev Dyn, 238 (2009) 2877-2890.
[15] R. Guerrini, E. Parrini, Neuronal migration disorders, Neurobiol Dis, 38 (2010) 154-166.
[16] S. Leigh, M. Futema, R. Whittall, A. Taylor-Beadling, M. Williams, J.T. den Dunnen, S.E. Humphries, The UCL low-density lipoprotein receptor gene variant database: pathogenicity update, J Med Genet, 54 (2017) 217-223.
[17] M. Chmara, B. Wasag, M. Zuk, J. Kubalska, A. Wegrzyn, M. Bednarska-Makaruk, E. Pronicka, H. Wehr, J.C. Defesche, A. Rynkiewicz, J. Limon, Molecular characterization of Polish patients with familial hypercholesterolemia: novel and recurrent LDLR mutations, J Appl Genet, 51 (2010) 95-106.

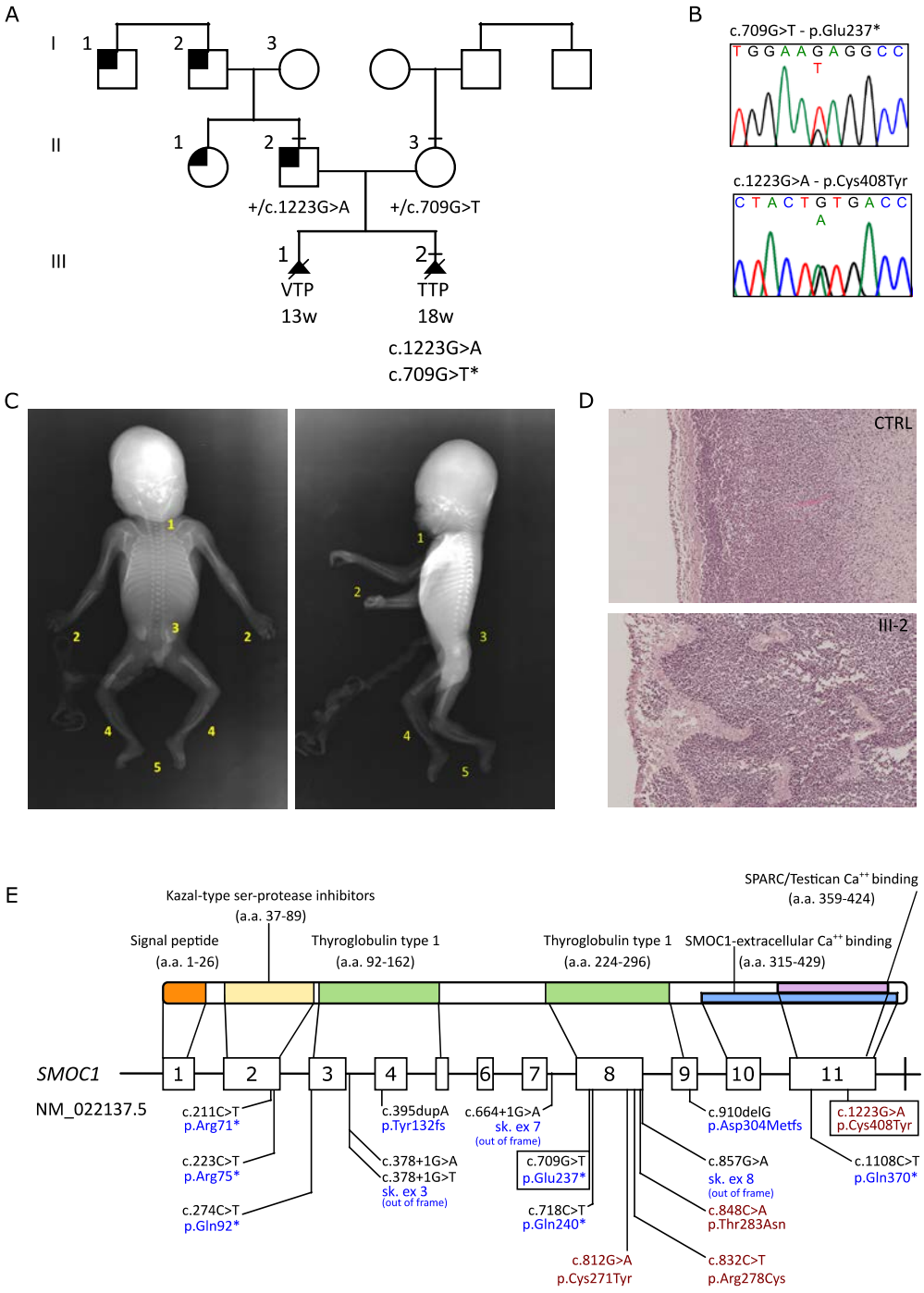
A
I
II
III
+/c.1223G>A
+/c.709G>T
VTP
13w
TTP
18w
c.1223G>A
c.709G>T*
B
c.709G>T - p.Glu237*
T G G A A G A G G C C
T
c.1223G>A - p.Cys408Tyr
C T A C T G T G A C C
A
C
D
CTRL
III-2
E
Kazal-type ser-protease inhibitors
(a.a. 37-89)
SPARC/Testican Ca++ binding
(a.a. 359-424)
Signal peptide
(a.a. 1-26)
Thyroglobulin type 1
(a.a. 92-162)
Thyroglobulin type 1
(a.a. 224-296)
SMOC1-extracellular Ca++ binding
(a.a. 315-429)
SMOC1
NM_022137.5
c.211C>T
p.Arg71*
c.223C>T
p.Arg75*
c.274C>T
p.Gln92*
c.395dupA
p.Tyr132fs
c.378+1G>A
c.378+1G>T
sk. ex 3
(out of frame)
c.664+1G>A
sk. ex 7
(out of frame)
c.709G>T
p.Glu237*
c.718C>T
p.Gln240*
c.812G>A
p.Cys271Tyr
c.910delG
p.Asp304Metfs
c.857G>A
sk. ex 8
(out of frame)
c.848C>A
p.Thr283Asn
c.832C>T
p.Arg278Cys
c.1223G>A
p.Cys408Tyr
c.1108C>T
p.Gln370*

Table 1. Comparison of clinical features of *SMOC1*-related MLA

							Ocular anomalies		Skeletal anomalies					
Case	Mutation 1	Mutation 2	Age	Sex	Geograph. Origin	Cons	Anophthalmia	Optic Nerve	Upper limbs	Lower limbs	Other	Cranio-facial	Other	PMID
1	c.211C>T; p.Arg71*	c.211C>T; p.Arg71*	7 Mo	F	Pakistani	Y	Unilat	-	-	Bilat postaxial ray defect		Pierre-Robin sequence		21750680
2	c.223C>T; p.Arg75*	c.223C>T; p.Arg75*	40 yrs	M	Calabrian	Y	Bilat	Absent	Bilat 4-5 metacarpal fusion	Bilat postaxial ray defect			Severe ID	21750680
3	c.274C>T; p.Gln92*	c.274C>T; p.Gln92*	11 yrs	F	Puertorican	N	Bilat	-	Fingers contracture	Bilat postaxial ray defect; Bilateral 2-3 cutaneous SYD	Bowed tibias, Talipes equino-varo		H-S kidney	21750680
4	c.378+1G>A (skipping ex.3)	c.378+1G>A (skipping ex.3)	-	F	Turkish	Y	Bilat	-	Syndactyly; 4-5 metacarpal fusion; CLD; Simian Crease	Bilateral OLD; Hypoplastic fibula		Arched Palate	FTT; Sacral dimple	21194678
5	c.378+1G>T (skipping ex.3)	c.378+1G>T (skipping ex.3)	12 yrs	F	Egyptian	Y	Bilat	Absent	Proximal thumb placement; 4-5 metacarpal fusion; CLD; CAD	Bilat ray defect	Mild scoliosis	Arched Palate	Global DD	21194680
6	c.395dupA; p.Tyr132fs*1	c.395dupA; p.Tyr132fs*1	6 Mo	M	Gipsy (Italian)	Y	Bilat	Remnants	Bilat 4-5 metacarpal fusion	Bilat postaxial ray defect	Bowed tibia		H-S kidney	21750680
7	c.664+1G>A (skipping ex.7)	c.664+1G>A (skipping ex.7)	-	M	Lebanese	Y	Bilat	Absent	CLD; CAD	Bilateral SYD			FTT; ID	21194678
8	c.709G>T; p.Glu237*	c.1223G>A; p.Cys408Tyr	-	M	Italian	N	Microphtalmia	-	Aracnodactily	Ray absence; tibial bowing	Cleft spine (lower lumbar and sacral)	Frontal bone depress.; Sliding of the posterior fossa content; Micro-gnatia	Abnor-mal cortical neuro-nal migra-tion	This report

9a	c.718C>T; p.Gln240*	c.718C>T; p.Gln240*	-	M	Japanese	-	Bilat	Absent	4-5 metacarpal fusion; CLD; CAD; Simian Crease	Bilateral OLD; Bowed tibia; Metatarsal synostosis; Pes valgus; 2-3 cutaneous SYD; Hypoplastic fibula			FTT; right cryptorchidism	21194678
9b	c.718C>T; p.Gln240*	c.718C>T; p.Gln240*	-	F	Japanese	-	Bilat	Absent	4-5 metacarpal fusion; Simian Crease	Bilateral OLD; Bowed tibia; metatarsal synostosis; 2-3 cutaneous SYD; hypoplastic fibula			FTT	21194678
10a	c.812G>A; p.Cys271Tyr	c.812G>A; p.Cys271Tyr	13 yrs	M	Pakistani	Y	Bilat	-	-	Pes planus; 2-5 syndactyly; Left postaxial polydactyly Bowed and hypoplastic tibia				28085523
10b	c.812G>A; p.Cys271Tyr	c.812G>A; p.Cys271Tyr	9 yrs	F	Pakistani	Y	Bilat	-	-	Pes planus; 2-5 fusion;			ID	28085523
10c	c.812G>A; p.Cys271Tyr	c.812G>A; p.Cys271Tyr	6 yrs	F	Pakistani	Y	Bilat	-	-	Left oligo-syndactyly; Right 2-5 fusion; Pes planus			Speech disorder	28085523
11	c.832C>T; p.Arg278Cys	c.832C>T; p.Arg278Cys	10 yrs	M	Sicilian	N	Bilat	Absent	CLD (5^{th})	4-5 cutaneous SYD		Arched palate	ID	21750680
12	c.848C>A; p.Thr283Asn	c.848C>A; p.Thr283Asn	14 yrs	M	Turkish	Y	Bilat	-	Short 5th metacarpal bone	2-5 cutaneous SYD; 4-5 metatarsal fusion				21750680
13a	c.857G>A; p.Arg286His	c.857G>A; p.Arg286His	13 yrs		Arabian	Y	Unilat	-	SYD				ID	23646827
13b	c.857G>A: p.Arg286His	c.857G>A; p.Arg286His	18 yrs		Arabian	Y	Bilat	-	SYD				ID	23646827
14	c.910delG; p.Asp304Metfs*59	c.910delG; p.Asp304Metfs*59	9 yrs	M	Lebanese	Y	Bilat	-	Cutaneous SYD; 5^{th} finger hypoplasia	Bilat. Postaxial ray defect; Cutaneous SYD		Cleft palate	H-S kidney; ID	21750680

										(2-4 left, 2-3 right)				
15	c.1108C>T ; p.Gln370*	c.1108C>T; p.Gln370*	18 yrs	M	Turkish	Y	Bilat	Absent	Bilat 4-5 metacarpal fusion; CAD; Elbows contracture	Bilat postaxial ray defect; Coxa valga			Severe ID; Epilepsy; Cryptorchidism	21750680

Mo: months; yrs: years; Cons.: consanguinity; CLD: clinodactyly; CAD: camptodactyly; SYD: syndactyly; OLD: olygodactyly; FTT: failure to thrive; ID: intellectual disability; H-S: horseshoe; DD: developmental delay; a dash (-) means the data was not reported in the referred paper.
Cases from the same family and identical phenotype were reported as a single entry. Cases from the same family with substantially different phenotype were reported with the same number followed by a letter (a-c).
Nomenclature of some mutations from PMID:21750680 has been changed to reflect the correct nucleotide/amino acid position.