Meta Gene 2 (2014) 72–82

Contents lists available at ScienceDirect

Meta Gene

Interstitial 12p deletion involving more than 40 genes in a patient with postnatal microcephaly, psychomotor delay, optic nerve atrophy, and facial dysmorphism ☆

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ARTICLE INFO

Article history:
Received 31 October 2013
Accepted 31 October 2013
Available online 11 January 2014

Keywords:
Microcephaly
Mental retardation
Array CGH

ABSTRACT

Interstitial deletions of chromosome 12p are rare, and the phenotype spectrum is therefore still unknown. The thirteen patients reported so far suffer from developmental delay, optic nerve hypoplasia, micropenis, hypoplastic hair and skin, oligodontia, brachydactyly, and arterial hypertension. We report a *de novo* 12p12.2–p11.22 deletion of 9.2 Mb detected by array CGH analysis in a boy with global developmental delay, muscular hypotonia, postnatal microcephaly, facial dysmorphism including small ears, epicanthus, broad nasal bridge and hypoplastic nostrils. In addition, the patient had optic nerve atrophy, inverted nipples, micropenis, and a hemangioma. The deleted region encompasses more than 40 reference genes. We compare phenotype and deletion extent of our index patient to that of previous reports and thereby contribute to the understanding of interstitial 12p deletion phenotypes.

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2214-5400/$ – see front matter
http://dx.doi.org/10.1016/j.mgene.2013.10.014

Knowledge of the pattern of this deletion phenotype will help clinicians to diagnose this abnormality in their patients and to counsel the parents accordingly. Further descriptions may be able to contribute to the clarification.

Introduction

Deletions of the short arm of chromosome 12 are rare with only thirteen patients reported since the first description of an infant carrying the deletion 12p11p13 in 1975 (Bahring et al., 1997; Boilly-Dartigalongue et al., 1985; Fryns et al., 1990; Glaser et al., 2003; Lu et al., 2009; Macdonald et al., 2010; Magenis et al., 1981; Magnelli and Therman, 1975; Malpuech G et al., 1975; Nagai et al., 1995; Orye and Craen, 1975; Soysal et al., 2011; Stumm et al., 2007; Tenconi et al., 1975). A number of common features of patients with interstitial 12p deletions have emerged including global delay, cardiac anomalies (AVSD, VSD, ASD II), microcephaly, and optic nerve atrophy (Table 1). Still, the spectrum of the clinical phenotype remains unknown. Here, we describe a boy with a *de novo* interstitial deletion of chromosome 12. We characterized the extent of the deletion by array CGH and compared the phenotypic characteristics of the patient with those of previously published case studies.

Material and methods

Karyotype

For chromosome analysis peripheral blood lymphocytes from the index patient, his brother, and his parents were karyotyped using standard protocols for cultivation and GTG banding at a level of 550 bands in accordance with the International System for Human Cytogenetic Nomenclature (ISCN) (Mitelman, 1995).

Array CGH analysis

We obtained blood samples from the index patient and his parents after written informed consent. Genomic DNA was isolated from peripheral blood lymphocytes according to standard procedures. Patient and female reference DNA (Promega, Mannheim, Germany) were labeled with Cy3 and Cy5 using the Genomic DNA Enzymatic Labeling Kit (Agilent, Santa Clara, CA) according to the manufacturer's protocol. The mixture was hybridized on a 180 K oligonucleotide array (Agilent, Santa Clara, CA) for 16 h in a hybridization oven. Image data were analyzed using Feature Extraction 9.5.3.1 and CGH Analytics 3.4.40 software (Agilent Technologies, Santa Clara, CA) with the following analysis settings: aberration algorithm ADM-2; threshold: 6.0; window size: 0.2 Mb; filter: 5 probes, log2ratio = 0.29. Genome coordinates are shown according to human genome build GRCh37(hg18).

Results

Phenotype

The boy is the second child of non-consanguineous and healthy parents of German descent (Fig. 1A). His mother reported two previous miscarriages and unilateral ear fistulas of two maternal half siblings. The index patient was born at term following an uneventful pregnancy without complications: birth weight 3390 g (40th centile; −0.22 SD), length 50 cm (35th centile; 0 SD), occipitofrontal head circumference (OFC) 34 cm (15th centile; −0.79 SD). He was first presented at 4 weeks-of-age for cyanotic spells, an eye movement disorder of intermittent exotropia and discrete anisocoria. At that time, a small persistent ductus arteriosus was diagnosed. At an age of eight months, he presented at our hospital because of a respiratory syncytial virus (RSV) bronchiolitis and an anal herpex simplex virus (HSV) 1 infection. On clinical investigation, he had significant psychomotor delay. Griffith testing revealed a developmental age of 10.5 months at the chronological age of 23.5 months (developmental quotient < 45%). Facial dysmorphism was noted *i.e.* small ears, epicanthus, broad nasal bridge, and hypoplastic nostrils (Fig. 1B, Supplemental Fig. 1). In addition, the patient showed a dystrophic

Table 1
Comparison of phenotype between index patient and previously reported patients with interstitial 12p deletions.
Abbreviations: m, male; f, female; y, year; mo, month; ADT, asphyxiating thoracic dystrophy.

Chromosome 12 segment	Age	Sex	Intellectual disability	Motor delay	Craniofacial dysmorphism	Micro-cephaly	Atrophy of optic nerve	Dental anomalies	Genital hypo-plasia	Skeletal anomalies	Digital anomalies	Cardio-vascular anomalies	Arterial Hyper-tension	Other	Reference
p11p13	2 mo	m	+	+	+						+	+			Tenconi et al. (1975)
p11p12.2	3 y	m	+	+	+	+					+				Malpuech G et al. (1975)
p11p12.1	17 y	f	+	+	+	+	+	+			+	+			Boilly-Dartigalongue et al. (1985)
p11.1p12.1	12 y	f	+		+	+		+		+	+				Soysal et al., 2011
p11.21p13.2	Fetus	f			+					+	+			Cystic pelvic kidney	Stumm et al. (2007)
p11.2p13.1	7.5 mo	f	+	+	+				+		+	+		Turner-like stigmata	Fryns et al. (1990)
p11.2p12.2	5 y	m	+		+			+			+		+	ATD	Nagai et al. (1995)
p11.21p12.2	6 y	m									+		+		Bahring et al. (1997)
p11.21p12.2	13 y	f	+		+	+		+			+		+		Lu et al. (2009)
p11.22p11.23	35 y	f									+			Short stature	Decipher 251557
p12.2p11.22	8 mo	m	+	+	+	+	+		+			+		Short stature, hemangioma	Our case
p12	13 mo	m	+	+	+	+	+	+			+				Orye and Craen (1975)
p12	6.5 y	m	+	+	+		+			+					Orye and Craen (1975)
p12.1p12.3	7	m	+	+	+	+				+		+		Hearing/ visual impairment	Glaser et al. (2003)
p12.1p12.3	11 y	m	+		+		+		+					Achalasia, apraxia	Decipher 139
p12.1	4 y	m	+			+									Decipher 253839
p12.3	28 mo	m	+	+	+	+									Magenis et al. (1981)
			14	9	14	9	5	6	3	5	11	5	3		Total (n = 17)

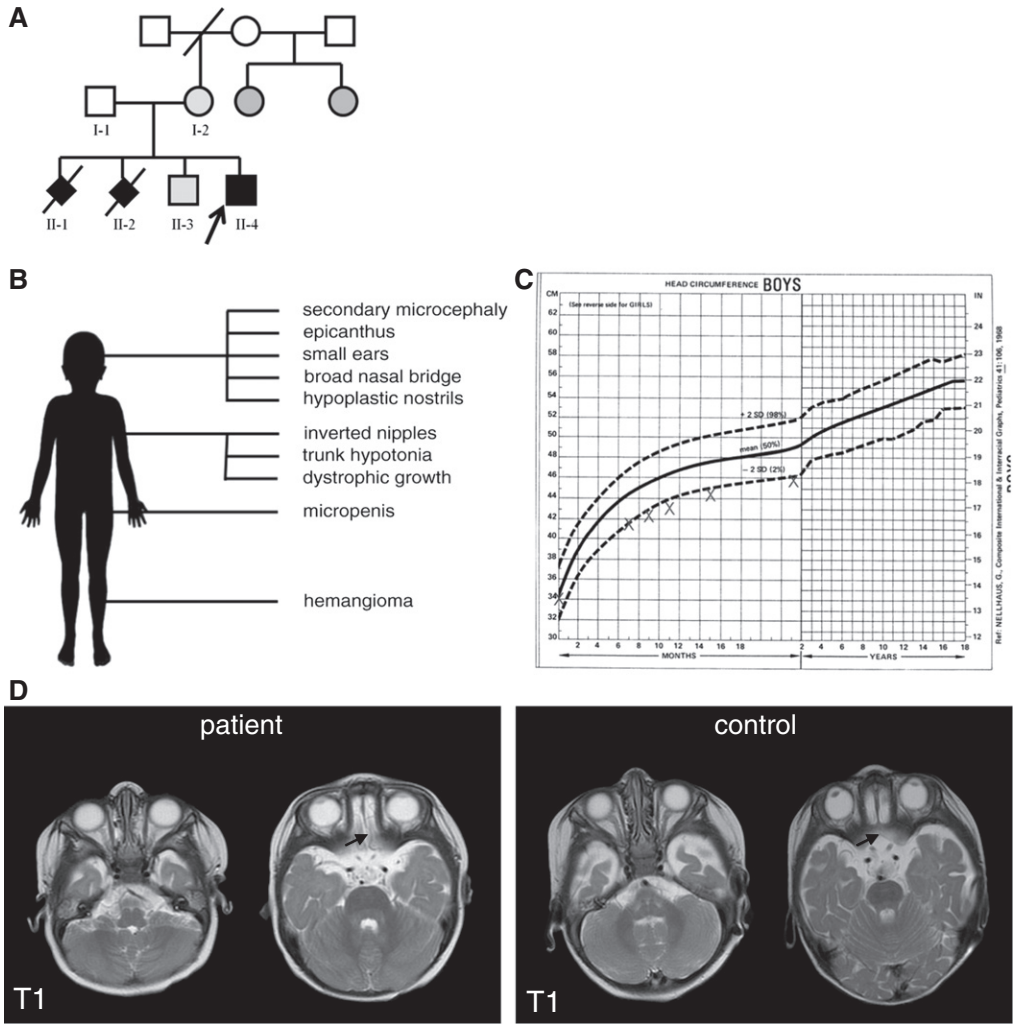

Fig. 1. Clinical and radiological phenotype of patient with 12p12.2–p11.22 deletion. (A) Pedigree; the patient's mother and brother showed a karyotype with a balanced Robertsonian translocation between chromosome 13 and 15 shown in gray shadings; (B) phenotype; (C) head circumference development illustrating postnatal microcephaly; (D) axial T1 cerebral MRI at the age of 8 months demonstrates bilateral optic nerve atrophy shown by a difference in the diameter of the intraorbital compared to the prechiasmal optic nerve (arrow) which is not present in an age-matched control.

growth at the age of 16 months: height 75.5 cm (0.5 cm <3rd centile, −1.48 SD), weight 9.78 kg (10th centile, −1.40 SD), a postnatal (secondary) microcephaly (OFC 44.4 cm (1 cm <3rd centile, −2.31 SD)) (Fig. 1C), inverted nipples, a micropenis, a hemangioma on his lower extremities (Fig. 1B) and trunk hypotonia. Results of routine laboratory tests, metabolic screening, electroencephalogram (EEG) and echocardiogram were normal. No seizures were reported. The patient had a normal bone age shown by X-ray without signs of brachydactyly type E and normotensive blood pressure values. Abdominal ultrasound revealed mild splenomegaly. VEP and cranial MRI showed evidence of bilateral optic atrophy (Fig. 1D). Radiation-induced chromosome fragility was increased significantly at 1.0 Gy, although not as high as in patients with ataxia telangiectatica or Nijmegen breakage syndrome.

Table 2
List of genes within deletion 12p12.2–p11.22.

Gene	Protein	OMIM	Function
SLCO1B3	Solute carrier organic anion transporter family, member 1B3	*605495	Hepatic uptake
SLCO1A2	Member 1A2	*147940	
SLCO1B1	Member 1B1	*604843	
RECQL	RECQ protein like	*600537	DNA repair helicase
ABCC9	ATP-binding cassette, subfamily C, member 9	*601439	ATP-sensitive potassium channel in heart and skeletal muscle
IAPP	Islet amyloid polypeptide	*147940	Role in pancreatic islet function, may be a factor in the etiology of the insulin resistance in type II diabetes mellitus
KCNJ8	Potassium channel, inwardly-rectifying, subfamily J, member 8	*600935	ATP-sensitive potassium channel in coronary artery smooth muscle and endothelial cells
PYROXD1	Pyridine nucleotide-disulphide oxidoreductase domain 1	–	Role in human male germ cell tumor differentiation
GOLT1B	Golgi transport 1B	*615078	Influences aspartate aminotransferase activity
GYS2	Glycogen synthase 2	*138571	Catalyzes rate-limiting step in glycogen synthesis
LDHB	Lactate dehydrogenase B	*150100	Enzymatic activator of glycolysis, catalyzes interconversion of lactate and pyruvate
CMAS	Cytidine 5-prime-monophosphatade N-acetylneuraminic acid synthetase	*603316	Activation of sialic acids, the terminal residues of cell surface glycoproteins and glycolipids
ST8SIA1	Alpha N-acetyl-neuraminide alpha 2-8-sialyltransferase 1	*601123	Ganglioside synthase, catalyzes GD3 ganglioside formation
ETNK1	Ethanolamine kinase 1	*609858	Catalyzes first step of phosphatidyl-ethanolamine synthesis pathway
SOX5	SRY-Box 5	*604975	Role in chondrogenesis, oligodendrocyte differentiation and migration
BCAT1	Branched-chain aminotransferase 1	*113520	Expressed early in embryogenesis, during organogenesis localized in neural tube, somites, and mesonephric tubules
LRMP	Lymphoid-restricted membrane protein	*602003	Expressed in a developmentally regulated manner in lymphoid tissues
KRAS	Kirsten rat sarcoma viral oncogene	*190070	Role in tissue signaling, including proliferation, differentiation, and senescence, mutated genes are oncogenes
CASC1	Cancer susceptibility candidate 1	–	Candidate *tumor suppressor gene* implicated in lung tumorigenesis
RASSF8	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	*608231	Role in maintaining adherens junction function in epithelial cells and has a role in epithelial cell migration, lung tumor suppressor gene candidate
BHLHE41	Basic helix-loop-helix family, member E41	*606200	Transcriptional, regulator of molecular clock, defects are associated with a short sleep phenotype
SSPN	Sarcospan	*601599	Links subsarcolemmal cytoskeleton and extracellular matrix of muscle cells
ITPR2	Inositol 1,4,5-trisphosphate receptor, type 2	*600144	Role in intracellular calcium response
FGFR1OP2	Fibroblast growth factor receptor 1 oncogene partner 2	*608858	May regulate cell motility and stimulate wound closure
TM7SF3	Transmembrane 7 superfamily member 3	*605181	Cell surface protein family, includes receptors for a variety of ligands
MED21	Mediator complex subunit 21	*603800	Multiprotein coactivator member required by DNA-binding transcription factors for activation of polymerase II-transcribed genes
STK38L	Serine/threonine kinase 38 like	–	Role in cell cycle, apoptosis
ARNTL2	Aryl hydrocarbon receptor nuclear translocator-like protein 2	*614517	Regulates circadian rhythm
PPFIBP1		*603141	

Table 2 (*continued*)

Gene	Protein	OMIM	Function
	Protein tyrosine phosphatase, receptor-type F interacting protein, binding protein 1		Interacts with proteins important for axon guidance and mammary gland development
MRPS35	Mitochondrial ribosomal protein S35	*611995	Role in mitochondrial protein synthesis
KLHDC5	Kelch domain containing protein 5	–	Role in mitosis
PTHLH	Parathyroid hormone-like hormone	*613382	Role in chondrocyte proliferation, mutation causes brachydactyly type E
CCDC91	Coiled-coil domain containing 91	–	Required for ciliogenesis
FAR2	Fatty acyl CoA reductase 2	–	Putative role in wax ester biosynthesis and in other pathways such as ether lipid synthesis
ERGIC2	Endoplasmic reticulum–Golgi intermediate compartment protein 2	*612236	Localized in nuclei of glandular epithelia, downregulated in prostate carcinoma
OVCH1	Ovochymase 1	–	Ovary-specific trypsin-like serine released during egg activation
TMTC1	Transmembrane and tetratricopeptide repeat containing 1	–	Role in protein adsorption and interfacial activity

Karyotype and array CGH

Conventional karyotyping indicated an interstitial deletion on the short arm of chromosome 12 [46,XY, del 12p11.2p12.?2]. To determine the size and the breakpoints more precisely we performed array CGH analysis using a high resolution oligonucleotide array. This analysis detected a 9.17 Mb deletion on chromosome 12p and thereby confirmed the previous results from karyotyping [arr[hg18] 12p12.2p11.22 (20,842,661-30,015,311)x1].

This region contains more than 40 known genes (Table 2) and extends from position 20.48 Mb to 30.01 Mb (Fig. 2). The patient's mother and brother showed a karyotype with a balanced Robertsonian translocation between chromosome 13 and 15.

Discussion

We report a patient with a *de novo* 9.2 Mb interstitial deletion on the short arm of chromosome 12 (12p12.2–p11.22) encompassing more than 40 reference genes. So far, ten other cases with interstitial deletions of the proximal part of chromosome 12 have been described (Bahring et al., 1997; Boilly-Dartigalongue et al., 1985; Glaser et al., 2003; Lu et al., 2009; Magenis et al., 1981; Malpuech G et al., 1975; Nagai et al., 1995; Orye and Craen, 1975; Soysal et al., 2011) and three patients with deletions extending more distally (Fryns et al., 1990; Lu et al., 2009; Tenconi et al., 1975). In the DECIPHER database (http://decipher.sanger.ac.uk) three additional cases with deletion 12p have been described (Table 1). When comparing the phenotype of the previously described cases with that of our patient, there is an overlap of clinical signs and symptoms such as psychomotor delay, microcephaly, facial dysmorphism including a flat nasal bridge and small ears, and ocular anomalies, particularly strabismus and bilateral optic nerve atrophy. These latter clinical signs and symptoms are unspecific and can be observed in association with various other chromosomal aberrations. We did not detect a correlation between the 12p deletion size or location and the clinical symptoms in the known cases including our index patient (Table 1, Fig. 3). Features reported previously in association with a 12p deletion but not present in our index patient were thoracic dystrophy, hair and skin changes, dental or skeletal anomalies, and borderline high blood pressure.

Malignancies

A putative increased risk for development of malignancies exists in view of the oncogenes and tumor suppressor genes within the deleted region of 12p in our index patient (Table 2). These genes are: *KRAS* (Kirsten rat sarcoma viral oncogene homolog, OMIM*190070), which regulates homeostasis and tumorgenesis in the colon (Haigis et al., 2008) and has been identified to hold mutations in patients with Noonan syndrome (OMIM#609942). *RECQL* (OMIM*600537), encoding for DNA repair helicase, plays a

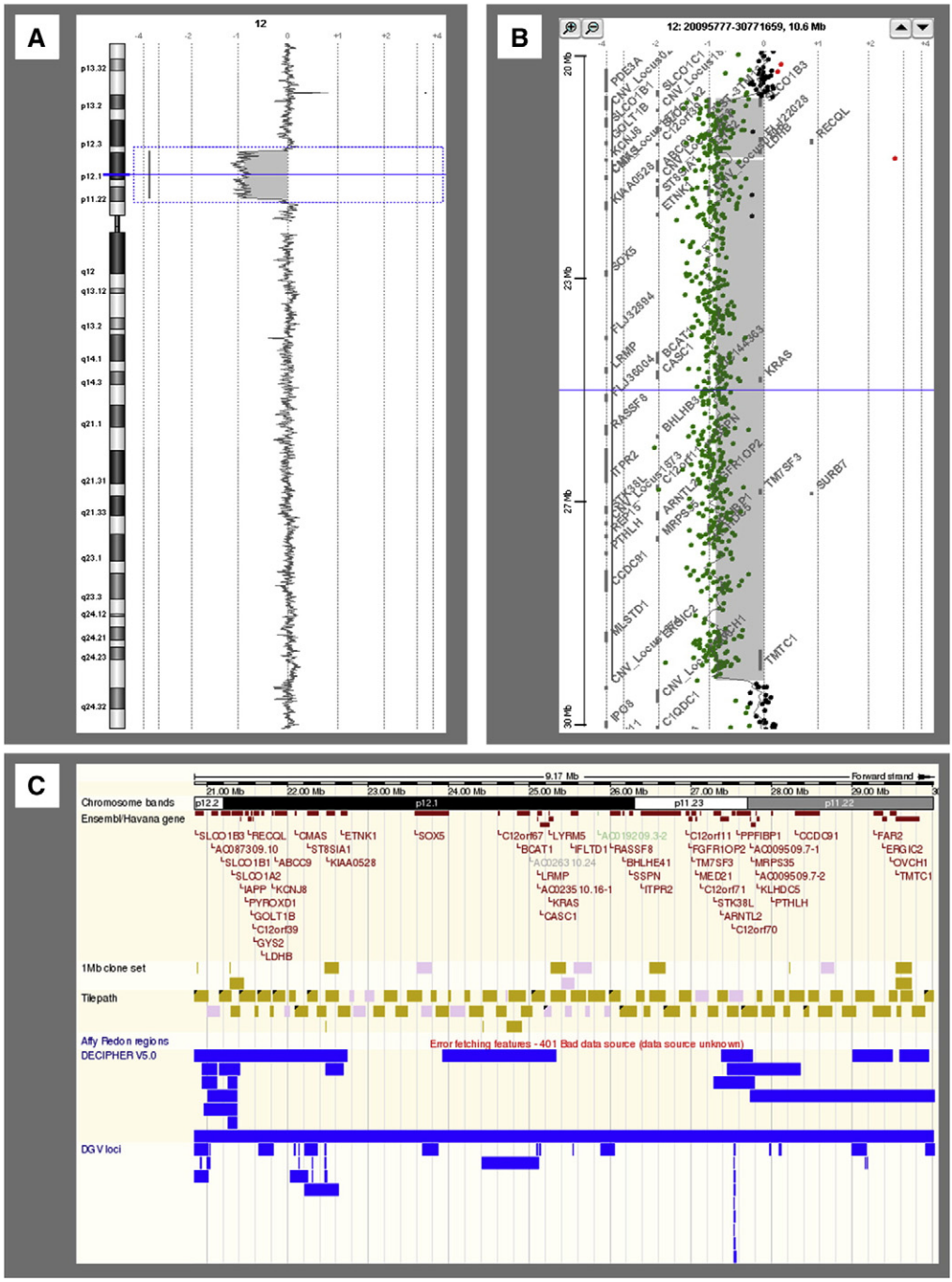

Fig. 2. Genes located within the deletion 12p12.2p11.22 (9.17 Mb). (A) Array CGH profile of chromosome 12 using Agilent's 180K. (B) Zoomed in version of panel A. The difference in copy number is measured by the same units in both plots. Interstitial deletion on chromosome 12p12.2p11.22 (log2ratio < −0.5). (C) Genes localized within the deleted region in our index patient according to Ensembl genome browser on human GRCh39/hg18.

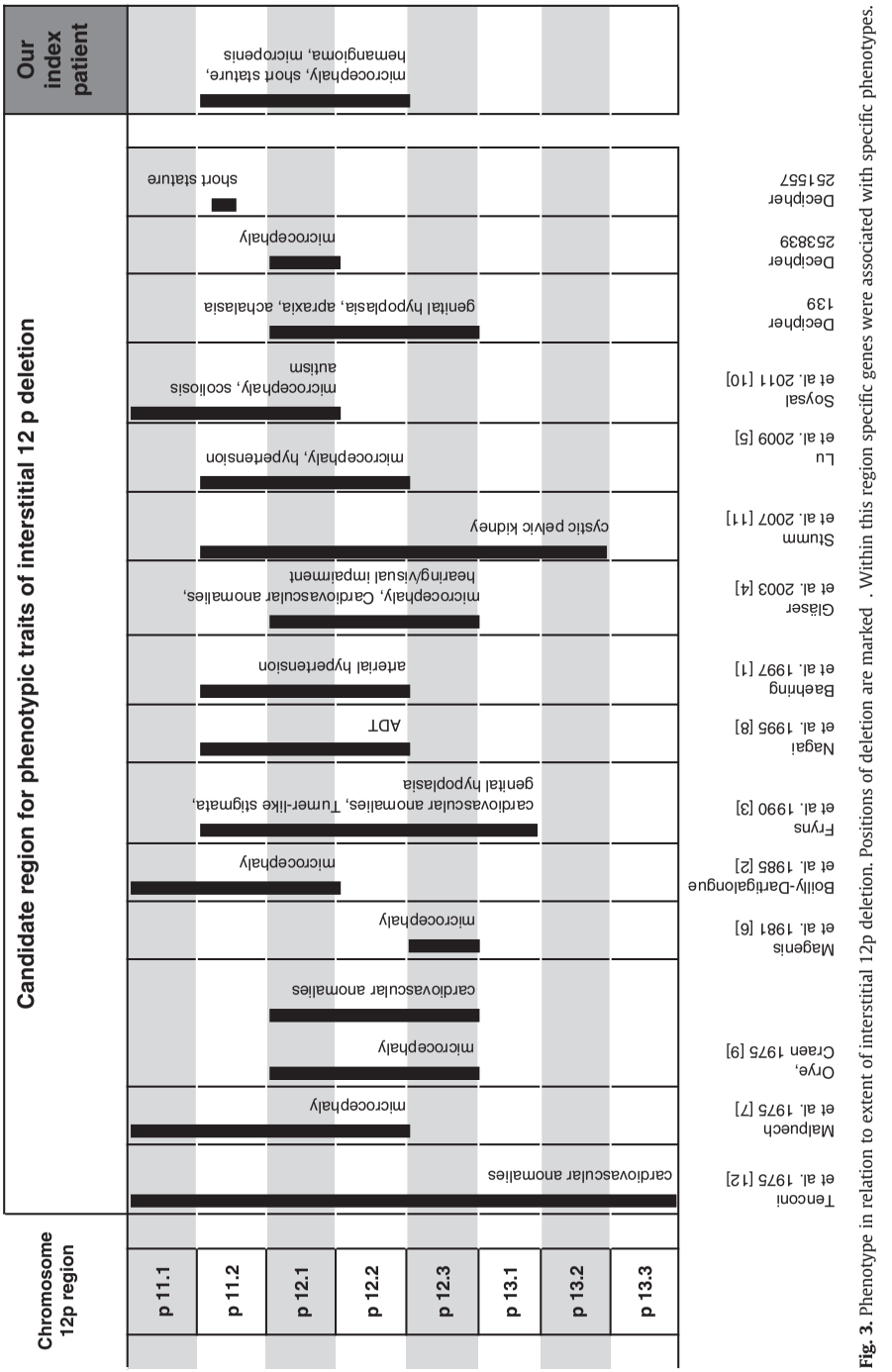

Fig. 3. Phenotype in relation to extent of interstitial 12p deletion. Positions of deletion are marked . Within this region specific genes were associated with specific phenotypes.

role in chromosome fragility. Mutations in similar genes such as *RECQL2*/3 cause autosomal recessive Bloom Syndrome (OMIM#210900) and Werner Syndrome (OMIM#2777700). Moreover, *CASC1* (cancer susceptibility candidate 1) polymorphisms have been described in several tumors, especially in lung cancer (Liu et al., 2003). Furthermore, there are a few *in vitro* data showing the importance of *RASSF8* (OMIM#608231) for mitosis (Falvella et al., 2006; Lock et al., 2010; Sherwood et al., 2009). *FGFR1OP2* (OMIM*608858) plays a role in the pathogenesis of myeloproliferative syndrome (Grand et al., 2004). *STK38L* is expressed in the process of squamous cell cancer development (Hummerich et al., 2006). *ERGIC2* (OMIM*612236) encodes a ubiquitously expressed nuclear protein that is down-regulated in prostate carcinoma (Liu et al., 2003). In addition, the short arm of chromosome 12 has been found to rearrange in a wide spectrum of leukemic cells. In a subgroup of hematologic malignancies, multiple chromosomal breaks in the 12p12 to p13 region result in the formation of rearrangements including translocations, inversion, and deletions (Sato et al., 2001). So far no malignancies have been reported in patients with 12p deletions. However, the reported children are very young, and we propose a long-term follow-up and analysis of chromosome instability in all cases.

Microcephaly

Eight of the reported thirteen patients in Table 1 presented with microcephaly, a clinical finding also present in our patient. This finding may be explained through a deletion of genes with an important role in the cerebral development but the case of Magenis et al. (1981) also showed microcephaly and this does not overlap with the deleted region in our index patient (Fig. 3). In our patient the mentioned genes could be responsible for microcephaly. One such gene is sarcospan *SSPN* (OMIM*601599; Kras oncogene-associated gene), a gene that encodes a dystrophin–glycoprotein complex (DGC) member and plays a role in hypoxia induced glial cell death (Zhou et al., 2008). Further genes to consider are the serine/threonine kinase 38 like, important for cell cycle and apoptosis gene *STK38L* (Cornils et al., 2011; Vichalkovski et al., 2008) and the *SOX5* gene (OMIM*604975, sex determining region Y-box 5). SOX genes are, in general, important for cell proliferation (Dugas et al., 2010), and SOX5 is, in particular, important for central nervous system development including oligodendrocyte differentiation and migration (Rosenfeld et al., 2010). Indeed, microcephaly is a recurrent feature in patients with 12p deletion but as mentioned above this can also be nonspecific. So far, none of the authors of other case reports specified the head circumference development. Postnatal microcephaly, as detected in our patient, could be secondary to apoptosis, as the patient did not display any evidence of a myelination disorder. It would be of interest to also differentiate between primary and secondary microcephaly in future reports.

Cardiovascular abnormalities

Four of the reported 13 patients display cardiovascular abnormalities not present in our patient, who only had a small PDA (persistent ductus arteriosus). There are two reference genes in the deleted region known to be associated with cardiovascular disorders: heterozygous mutations in *ABCC9* (ATP-binding cassette, sub-family C member 9; OMIM*601439) cause dilated cardiomyopathy (Bienengraeber et al., 2004), and heterozygous deletions of *PTHLH* (OMIM+168470) can cause brachydactyly type E (OMIM#613382) and can be associated with arterial hypertension (Klopocki et al., 2010). Therefore, patients with deletion 12p need to be screened for abnormal blood pressure and pathological echocardiogram.

Microdeletion 12p

Analysis of G-banded metaphase chromosomes from the patient showed the presence of an interstitial deletion of the short arm of chromosome 12: karyotype 46XY, del(12)(p11.2p12.2). We performed array-CGH analysis to refine the extent of the deletion. This revealed a *de novo* interstitial deletion of 9.2 Mb in the 12p12.2-p11.22 region (chr12: 20,842,661-661-30,015,311, hg18), which contains more than 40 known genes (Table 2) and extends from position 20.48 Mb to 30.01 Mb (Fig. 2). The deletions of previously examined patients were determined merely by G-banding analysis. In the present study, we determined the extent of the deletion of our patient by array CGH to encompass about 9.2 Mb. It is a future task of clinical cytogenetics to more precisely characterize structural aberrations in order to define more clearly the cases with similar imbalances, which then can be studied with respect to phenotype and clinical

variability. With our case report, we contribute to the understanding of the phenotype of patients with interstitial deletions of chromosome 12p. Knowledge of the pattern of this deletion-phenotype will help clinicians to diagnose this abnormality in their patients and to counsel the parents accordingly. Further descriptions may be able to contribute to the clarification.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.mgene.2013.10.014.

Acknowledgments

The authors thank the patient and his family for participating in this study and acknowledge Theodor Michael and Christoph Hübner for discussion.

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