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, micro-penis, 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.

Keywords: Microcephaly Mental retardation Array CGH

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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.

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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; Frys et al., 1990; Glaser et al., 2003; Lu et al., 2009; Macdonald et al., 2010; Magenis et al., 1981; Magnelli and Theram, 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 arterioso 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 | Microcephaly | Atrophy of optic nerve | Dental anomalies | Genital hypoplasia | Skeletal anomalies | Digital anomalies | Cardiovascular anomalies | Arterial Hypertension | 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   | +                        | +           | +                        |              |                        | +               | +                 | +                 | +               |                            |                           |                                | Stumm et al. (2007)                   |
| p11.2p13.1            | 7.5 mo | f   | +                        | +           | +                        |              |                        | +               | +                 | +                 | +               |                            |                           |                                | Fryns et al. (1990)                   |
| p11.2p12.2            | 5 y   | m   | +                        | +           | +                        |              |                        | +               | +                 | +                 | +               |                            |                           |                                | 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   | +                        | +           | +                        |              |                        | +               | +                 | +                 | +               |                            |                           |                                | Decipher 251557                      |
| p12.2p11.22           | 8 mo  | m   | +                        | +           | +                        | +            | +                      | +               | +                 | +                 | +               |                            |                           |                                | Our case                           |
| p12                   | 13 mo | m   | +                        | +           | +                        | +            | +                      | +               | +                 | +                 | +               |                            |                           |                                | Orye and Craen (1975)                |
| p12                   | 6.5 y | m   | +                        | +           | +                        |              |                        | +               | +                 | +                 | +               |                            |                           |                                | Orye and Craen (1975)                |
| p12.1p12.3            | 7     | m   | +                        | +           | +                        | +            |                        | +               | +                 | +                 | +               |                            |                           |                                | Glaser et al. (2003)                 |
| p12.1p12.3            | 11 y  | m   | +                        | +           | +                        | +            |                        | +               | +                 | +                 | +               |                            |                           |                                | Decipher 139                        |
| p12.1                 | 4 y   | m   | +                        | +           | +                        |              |                        | +               | +                 | +                 | +               |                            |                           |                                | Decipher 253839                     |
| p12.3                 | 28 mo | m   | +                        | +           | +                        |              |                        | +               | +                 | +                 | +               |                            |                           |                                | Magenis et al. (1981)                |

Total (n = 17)
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.

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.
| Gene     | Protein                                           | OMIM  | Function                                                                                     |
|----------|---------------------------------------------------|-------|---------------------------------------------------------------------------------------------|
| **SLCO1B3** | Solute carrier organic anion transporter family, member 1B3 | *605495 | Hepatic uptake                                                                               |
| **SLCO1A2** | Member 1A2                                       | *147940 |                                               |
| **SLCO1B1** | Member 1B1                                       | *604843 |                                               |
| **RECO** | RECO protein like                                | *600537 | DNA repair helicase                                                                          |
| **ABC9** | 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       |
| **PYROX1D1** | Pyridine nucleotide-disulphide oxidoreductase domain 1 | – | Role in human male germ cell tumor differentiation                                           |
| **GOL1B** | Golgi transport 1B                                | *615078 | Influences aspartate aminotransferase activity                                              |
| **GYS2** | Glycogen synthase 2                               | *136571 | 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-monophosphatase 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              | *600300 | 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                   |
| **ITP2R2** | 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                  | *614517 | Regulates circadian rhythm                                                                  |
| **ARNL2** | Aryl hydrocarbon receptor nuclear translocator-like protein 2 | – | Role in cell cycle, apoptosis                                                               |
| **PPFIBP1** |                                            | *603141 |                                               |
Karyotype and array CGH

Conventional karyotyping indicated an interstitial deletion on the short arm of chromosome 12 [46,XY, del 12p11.2p12.22]. 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 tumorigenesis 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

Table 2 (continued)

| Gene          | Protein                                                                 | OMIM      | Function                                                                 |
|---------------|------------------------------------------------------------------------|-----------|-------------------------------------------------------------------------|
| MRPS35        | Mitochondrial ribosomal protein S35                                    | *611995   | Role in mitochondrial protein synthesis                                 |
| KIAHDC5       | Keilch domain containing protein 5                                     | –         | Role in mitosis                                                         |
| FHHL          | Parathyroid hormone-like hormone                                       | *613382   | Role in chondrocyte proliferation, mutation causes brachydactyly type E |
| CCDC91        | Coiled-coil domain containing 91                                       | –         | Putative role in wax ester biosynthesis and in other pathways such as   |
| FAR2          | Fatty acyl CoA reductase 2                                             | –         | ether lipid synthesis                                                   |
| ERGIC2        | Endoplasmic reticulum–Golgi intermediate compartment protein 2         | *612236   | Localized in nuclei of glandular epithelia, downregulated in prostate   |
| 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                     |

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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.
Chromosome 12p region

Candidate region for phenotypic traits of interstitial 12p deletion

| Patient | Microcephaly | Cardiovascular anomalies | Hearing/Visual impairment | Turner-like stigmata | Genital hypoplasia | Autism |
|---------|--------------|--------------------------|---------------------------|----------------------|--------------------|-------|
| Index   |              |                          |                           |                      |                    |       |

Our index patient

Index patient

Fig. 3. Phenotype in relation to extent of interstitial 12p deletion. Positions of deletions are marked. Within this region specific genes were associated with specific phenotypes.
role in chromosome fragility. Mutations in similar genes such as \textit{RECQL2/3} cause autosomal recessive Bloom Syndrome (OMIM\#210900) and Werner Syndrome (OMIM\#2777700). Moreover, \textit{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 \textit{in vitro} data showing the importance of \textit{RASSF8} (OMIM\#608231) for mitosis (Falvella et al., 2006; Lock et al., 2010; Sherwood et al., 2009). \textit{FGFR1OP2} (OMIM\#608858) plays a role in the pathogenesis of myeloproliferative syndrome (Grand et al., 2004). \textit{STK38L} is expressed in the process of squamous cell cancer development (Hummerich et al., 2006). \textit{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 \textit{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 \textit{STK38L} (Cornils et al., 2011; Vichalkovski et al., 2008) and the \textit{SOX5} gene (OMIM\#604975, sex determining region Y-box 5). SOX genes are, in general, important for cell proliferation (Dugas et al., 2010), and \textit{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 \textit{ABCC9} (ATP-binding cassette, sub-family C member 9; OMIM\#601439) cause dilated cardiomyopathy (Bienengraeber et al., 2004), and heterozygous deletions of \textit{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 \textit{de novo} interstitial deletion of 9.2 Mb in the 12p11.22 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.

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