SHORT REPORT

Osteopoikilosis, short stature and mental retardation as key features of a new microdeletion syndrome on 12q14

Björn Menten, Karen Buysse, Farah Zahir, Jan Hellemans, Sara J Hamilton, Teresa Costa, Carrie Fagerstrom, George Anadiotis, Daniel Kingsbury, Barbara C McGillivray, Marco A Marra, Jan M Friedman, Frank Speleman, Geert Mortier

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This report presents the detection of a heterozygous deletion at chromosome 12q14 in three unrelated patients with a similar phenotype consisting of mild mental retardation, failure to thrive in infancy, proportionate short stature and osteopoikilosis as the most characteristic features. In each case, this interstitial deletion was found using molecular karyotyping. The deletion occurred as a de novo event and varied between 3.44 and 6 megabases (Mb) in size with a 3.44 Mb common deleted region. The deleted interval was not flanked by low-copy repeats or segmental duplications. It contains 13 RefSeq genes, including *LEMD3*, which was previously shown to be the causal gene for osteopoikilosis. The observation of osteopoikilosis lesions should facilitate recognition of this new microdeletion syndrome among children with failure to thrive, short stature and learning disabilities.

Classical cytogenetic analysis has played an essential role in the discovery of recurrent segmental deletions in patients with clinically recognisable mental retardation such as Prader–Willi, Miller–Dieker, Langer–Giedion and velocardiofacial syndromes.[1] The subsequent delineation of commonly deleted segments and mapping of small atypical deletions have allowed the identification of genes responsible for the major clinical features of these contiguous gene deletion syndromes.[2] Recently, molecular karyotyping was proven to be a more powerful tool in detecting submicroscopic deletions or duplications in patients with so-called idiopathic mental retardation with or without congenital malformations. Molecular karyotyping studies have shown that in about 10% of these cases segmental imbalances can be found.[3–9] Using this new genome-wide screening technology, new disease genes can be identified, as illustrated for the *CHD7* gene in CHARGE syndrome.[10] Very recently, some new microdeletion syndromes were identified using molecular karyotyping.[11–13]

Here, we report on three unrelated patients with de novo 12q14 microdeletions. They share osteopoikilosis, short stature and learning disabilities as common phenotypic features. In two cases the deletion was approximately 6 megabases (Mb) in size whereas in the third patient a 3.44 Mb deletion was detected.

The first proband (03g1858) is a girl born at term with a birth weight of 2060 g. Pregnancy and delivery were uneventful. At the age of 6 months, she presented with failure to thrive and by the age of 1 year, length, weight and head circumference were all far below the third centile. Work-up for this failure to thrive only revealed hypertension, for which she received medication. The diagnosis of Russell-Silver syndrome was considered at that time. The girl also showed delayed neuromotor development and experienced learning difficulties requiring an individualised programme at school. Clinical evaluation at the age of 16 years revealed proportionate short stature with a weight of 31.8 kg (−4 SDs), height of 131.5 cm (−6.2 SDs), span of 131 cm and head circumference of 49 cm (−4.4 SDs). The face was mildly dysmorphic with synophrys, mild hypertelorism, broad and high nasal bridge, micrognathia and maxillary overbite. These clinical features were not reminiscent of Russell-Silver syndrome. Imaging studies revealed the presence of ectopic kidneys, and an aortogram showed on each side two renal arteries with an aberrant origin. In addition, malrotation of the small bowel, a medially positioned spleen and an unusually shaped (rectangular) liver were found. Radiographic evaluation showed multiple osteopoikilosis lesions in the pelvis, shoulders, wrists, hands and feet (fig 1A).

The second female proband (D0502619, figure 1B,C) was born at term with a weight of 2300 g. The pregnancy was complicated by oligohydramnios. The postnatal course was uneventful. Early in infancy very poor growth and development became apparent. At the age of 4 years she was diagnosed with scoliosis, type 1 Arnold-Chiari malformation and ultimately syringomelia requiring a shunt. She also had a release for a tethered spinal cord. Reflux nephropathy with small kidneys, mild hypertension and diabetes mellitus were diagnosed in childhood. In school, mild learning problems became apparent, and therefore she was put on an individualised education plan. At the age of 14 years she presented with complaints of tingling pain in the medial part of her right foot. Clinical evaluation revealed a weight of 51.3 kg (mean for age), height of 142.3 cm (−3.5 SDs) and head circumference of 53.3 cm (−0.66 SDs). Her face was round with rather deep-set eyes, bushy eyebrows and thin lips. (fig 1B,C). A thoracolumbar scoliosis was noted. The skin showed several areas of increased pigmentation. Mild swelling without other inflammatory signs was present on the right foot. The gait pattern was somewhat antalgic. Radiographic evaluation revealed numerous osteopoikilosis lesions in the distal part of the tibia and fibula as well as in the right foot. In addition, the second right metatarsal showed a thickened and irregular cortical lesion suggestive of melorheostosis at the diaphysis. At the age of nearly 16 years, she is now functioning at the level of a 10-year-old child. She is quite sociable and tends to be very articulate and repetitive.

The third patient (#4818) is the male product of the first pregnancy of an unrelated 22-year-old mother and 35-year-old father. The pregnancy was complicated by hyperemesis. There were no adverse exposures. The family history was non-contributory. Delivery was at term with weight at the third centile and length at the tenth centile. The boy failed to thrive during the first year. At age three years six months, all growth measurements were below the third centile, and development was a year delayed. Growth hormone levels and bone age were normal. At age four, he was found to have delays in fine motor

Abbreviations: FISH, fluorescence in situ hybridisation; Mb, megabase

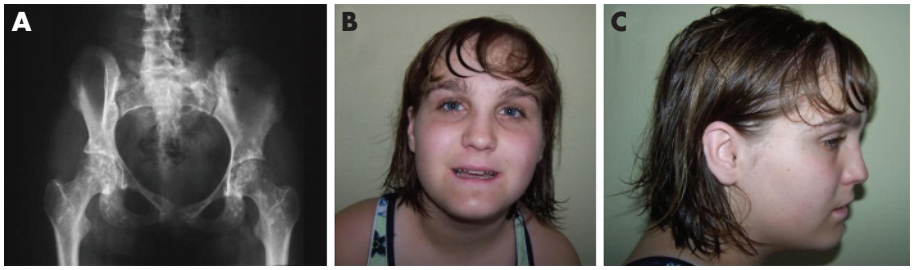

Figure 1 Clinical and radiographic features of the microdeletion syndrome. (A) Radiograph of the pelvis in patient 03g1858 showing multiple osteopoikilosis lesions in the proximal parts of the femurs and pubic bones. Facial phenotype of patient D0502619 with anteroposterior (B) and lateral (C) view (patients 03g1858 and #4818 refused clinical photographs). Parental/guardian informed consent was obtained for publication of this figure.

skills and speech. Six secondary teeth were missing on dental radiographs. After sustaining a fracture of the right tibia, he developed clawing of the toes and electromyogram findings suggestive of sciatic nerve injury. Radiographs documented osteopoikilosis lesions within multiple bones. When seen at 12 years of age, he was noted to have mild developmental delay, with difficulties in spelling and reading. He was tiny, with all growth measurements below the third centile. His face was triangular with widely spaced eyes. There were yellowish raised areas on the skin overlying the upper chest and flank. Trichothiodystrophy was considered as a diagnosis, but his hair was normal. He was reported to have a tremor that increased with writing. The patient was seen again at 18 years of age. His final height of 152 cm and weight of 41 kg were both below the third centile. He described a slow increase in tremor, most marked upon arising or intention. His overall health had been good, and he had achieved a normal puberty. He was entering grade 12, taking applied mathematics, and having problems with English.

The microdeletion in the first proband (03g1858) was identified during the course of mapping the gene for osteopoikilosis.[14] The patient showed loss of heterozygosity for a stretch of markers in the linkage interval, which resulted in a considerable reduction of the critical region and finally led (through a candidate gene approach) to the identification of *LEMD3* as the causal gene for osteopoikilosis. The deletion was confirmed with fluorescence in situ hybridisation (FISH) using BAC clone RP11-305O6, as described by Van Roy *et al*.[15] Breakpoints were further delineated using array CGH as described by Menten *et al*[16] with a custom tiling path array for chromosomal bands 12q14–12q15. BAC clones were selected based upon the May 2004 human genome project assembly (http://genome.ucsc.edu/) (table 1, appendix).

After publication of the first patient, a second patient with a similar phenotype was identified. FISH with BAC clones RP11-305O6 and RP11-361O1 confirmed the presence of a microdeletion encompassing *LEMD3* on chromosome 12. As in the first proband, the size of the deletion and the position of the breakpoints were determined by array CGH using a custom tiling path array with overlapping BAC clones (fig 2). The size of the deletion in the first two cases was similar (about 6 Mb) with an overlap of about 5.3 Mb. The genomic position of the deletion in patient 1 was slightly more telomeric than that in patient 2. Karyotyping and FISH of the parents of patients 1 and 2 yielded normal results, indicating that both deletions occurred de novo.

The microdeletion in the third patient (#4818) was identified during a study of 100 children with idiopathic mental retardation and normal standard chromosomal analysis, using Affymetrix GeneChip® Human Mapping 100K arrays.[9] Breakpoints were mapped to SNP rs10506536 (63342649 base pairs) and SNP rs10492198 (66780095 base pairs), indicating a 3.44 Mb deletion. Affymetrix Genechip® analysis of the parents yielded normal results, indicating that this deletion also occurred de novo. The deletion in the child was confirmed by FISH using BAC RP11-91K23. This deletion is smaller but lies entirely within the 5.3 Mb region that was deleted in both patients 1 and 2 (fig 2).

Segmental duplications or low copy repeats have been shown to play an important role in the formation of recurrent microdeletion syndromes by non-allelic homologous recombination.[17–20] However, no evidence of segmental duplications or low-copy repeats was found near any of the six breakpoints in these three patients. Microdeletions may also occur without involvement of low copy repeats.[12 21–23] Recent reviews estimate that only 25–50% of copy-number variants are associated with segmental duplications.[24] Recurrent microdeletions that are not associated with low-copy repeats usually have different breakpoints in each case. They most likely result from breakage with subsequent nonhomologous endjoining. Given the apparent absence of low copy repeats near the 12q breakpoints described here, we suspect that a mechanism of nonhomologous endjoining may be responsible for occurrence of the microdeletions in our three cases.

In 1995, Jurenka and Van Allen reported a patient with mental retardation, short stature and a mixed sclerosing bone dysplasia reminiscent of melorheostosis.[25] We suspect that this patient may have the same microdeletion as found in our three probands. Unfortunately, no DNA from this patient was available to test this hypothesis.

The similar phenotype in our three probands is remarkable. All three patients had a low birth weight and presented in infancy with failure to thrive. They subsequently showed delayed neuromotor development and finally mild mental retardation. They do not show a remarkable facial dysmorphism but all have a proportionate short stature with osteopoikilosis lesions on skeletal radiographs. One patient (#D0502619) developed a melorheostosis lesion in the foot. We have shown in previous studies that loss-of-function mutations in the *LEMD3* gene can result in osteopoikilosis and/or melorheostosis lesions.[14 26] However, failure to thrive, short stature and mental retardation are not observed in patients with either osteopoikilosis or melorheostosis. These findings must therefore be the result of haploinsufficiency for other contiguous genes in the microdeletion interval. In the common deleted region two interesting genes (*HMGA2* and *GRIP1*) reside, which may account for these additional clinical problems in our patients (fig 2).

HMGA2 codes for an architectural factor belonging to the high-mobility group (HMG) of proteins. It is characterised by three conserved DNA-binding domains, AT hooks and an acidic C-terminal tail. This gene product is involved in DNA packaging and plays an important role as a transcription factor in gene regulation.[27] Recently, *HMGA2* was described as the putative causal gene in a patient with overgrowth, lipomas and a de novo pericentric inversion of chromosome 12.[28] Battista *et al* reported a murine model with a constitutively expressed truncated form of *Hmga2*, which led to gigantism associated with lipomatosis. The authors proposed that disruption of the *Hmga2* gene led to upregulated expression.[29] Disruptions and

Table 1 BAC clones used for breakpoint detection in patients 1 and 2, with their name, sanger name, chromosome, start position and end position according to the NCBI 36 genome assembly

Name	Sanger name	Chromosome	Start (base pairs)	End (base pairs)	Patient 1	Patient 2
RP11-103L8	bA103L8	12	60326906	60482957	+	+
RP11-96F13	bA96F13	12	60399378	60556846	+	+
RP11-402I16	bA402I16	12	60470226	60639036	+	+
RP11-196A13	bA196A13	12	60516544	60670139	+	+
RP11-15P10	bA15P10	12	60592183	60768715	+	+
RP11-542G14	bA542G14	12	60637601	60804185	+	+
RP11-155D5	bA155D5	12	60695975	60861269	+	+
RP11-120M24	bA120M24	12	60829050	60980979	+	+
RP11-97A6	bA97A6	12	60917552	61052698	+	+
RP11-169M9	bA169M9	12	60920103	60948010	+	+
RP11-467D14	bA467D14	12	60966290	61162052	+	−
RP11-142E5	bA142E5	12	61085454	61271298	+	−
RP11-151H22	bA151H22	12	61221704	61367847	+	−
RP11-570O18	bA570O18	12	61280315	61431623	+	−
RP11-131G23	bA131G23	12	61343791	61525936	+	−
RP11-538D3	bA538D3	12	61529122	61684800	+	−
RP11-24L23	bA24L23	12	61634279	61805538	−	−
RP11-263K23	bA263K23	12	61706479	61872677	−	−
RP11-61L21	bA61L21	12	61883235	61951183	−	−
RP11-105I10	bA105I10	12	61907586	62065780	−	−
RP11-52P5	bA52P5	12	62021250	62183689	−	−
RP11-267F23	bA267F23	12	62033781	62189805	−	−
RP11-134D22	bA134D22	12	62196683	62347713	−	−
RP11-272A21	bA272A21	12	62218641	62371090	−	−
RP11-415I12	bA415I12	12	62349962	62538439	−	−
RP11-367H3	bA367H3	12	62470168	62644125	−	−
RP11-274J7	bA274J7	12	62508196	62670790	−	−
RP11-456A6	bA456A6	12	62577649	62745265	−	−
RP11-196H14	bA196H14	12	62738094	62928731	−	−
RP11-290I21	bA290I21	12	62854244	62854997	−	−
RP11-444B24	bA444B24	12	66740902	66931728	−	−
RP11-71J4	bA71J4	12	66926693	67077364	−	+
RP11-81H14	bA81H14	12	67059831	67208966	−	+
RP11-185H13	bA185H13	12	67160267	67368737	−	+
RP11-254B13	bA254B13	12	67191207	67347334	−	+
RP11-531F4	bA531F4	12	67255471	67462087	−	+
RP11-450G15	bA450G15	12	67366710	67543065	−	+
RP11-410I6	bA410I6	12	67507773	67668188	−	+
RP11-249J13	bA249J13	12	67574683	67726286	−	+
RP11-43A22	bA43A22	12	67681180	67830736	+	+
RP11-324P9	bA324P9	12	67816914	68000647	+	+
RP11-73J11	bA73J11	12	67862072	68020699	+	+
RP11-426B12	bA426B12	12	67926203	68135266	+	+
RP11-159A18	bA159A18	12	68032940	68179706	+	+
RP11-23C15	bA23C15	12	68135291	68315468	+	+
RP11-15L3	bA15L3	12	68217524	68403913	+	+
RP11-161M18	bA161M18	12	68369051	68562065	+	+
RP11-21I1	bA21I1	12	68442353	68627676	+	+
RP11-21C8	bA21C8	12	68508458	68666217	+	+
RP11-384F11	bA384F11	12	68610540	68808607	+	+
RP11-60E14	bA60E14	12	68706960	68858931	+	+

+, Presence of two copies; −, the BAC clone is deleted according to the array CGH profile.

rearrangements of *HGMA2* leading to aberrant gene expression are a frequent observation in lipomas and other benign mesenchymal tumours.[30–37] Overexpression has also been reported in malignant tumours.[38] Interestingly, Zhou *et al*. reported a ''pygmy'' phenotype in *Hmga2*$^{-/-}$ murine models,[39] with heterozygous mice displaying a milder phenotype (80% of the weight of wild-type mice).[40] Taken together, these data are consistent with an important role for *HMGA2* in growth. Hence, haploinsufficiency of this gene may result in short stature as observed in our patients. To test this hypothesis, a series of patients with idiopathic proportionate short stature will be tested for loss-of-function mutations in the *HMGA2* gene.

Glutamate receptor interacting protein 1 (*GRIP1*) is a good candidate gene for mental retardation. *GRIP1* is highly expressed in adult human and fetal brain as well as in other organ systems. The gene produces three different transcripts by alternative splicing and contains seven highly conserved domains. All *GRIP1* products contain the PDZ domain, which is important in synaptic function.[41] *GRIP1* proteins localise through their PDZ domains to α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors in cultured rat hippocampal neurons.[42 43] These AMPA receptors mediate synaptic transmission through glutamate, the major excitatory neurotransmitter in the central nervous system. *GRIP1* is implicated in targeting AMPA receptors to the synapse.[42 44 45] *GRIP1* is also involved in the induction of long-term potentiation in rat hippocampal mossy fibres.[46] In addition to their role in glutamergic synaptic transmission, *GRIP1* products also localise to GABAergic synapses in rat hippocampal cultures and intact rat brain.[47 48] Homozygous Grip1 knockout mice die as embryos.[49] The heterozygous *Grip1* knockout mouse phenotype has not yet been reported. The observations that *GRIP1* codes for a non-redundant protein that it is highly expressed in fetal and adult human brain, and involved in glutamergic synaptic transmission, support the possibility that *GRIP1* haploinsufficiency caused the learning problems in our patients.

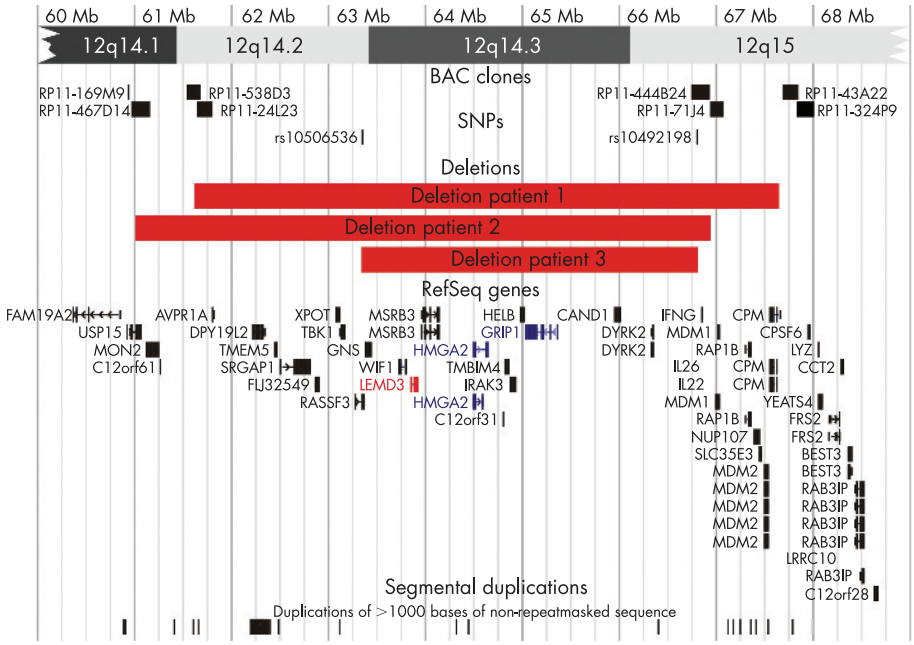

Figure 2 Chromosomal map of the deleted region with breakpoint flanking BAC clones for patients 1 and 2, breakpoint flanking SNP markers for patient 3, RefSeq genes (UCSC Genome Browser on Human Mar. 2006 Assembly) and segmental duplications. Karyotypes are written as: 46,XX,del(12)(q14.2q15).ish del(12)(q14.3)(RP11-305O6-) arr cgh 12q14.2q15(RP11-24L23RP11-249J13)x1 de novo for patient 1, 46,XX,del(12)(q14.1q15).ish del(12)(q14.3)(RP11-305O6-,RP11-361O1-) arr cgh 12q14.1q15(RP11-467D14 RP11-444B24)x1 de novo for patient 2 and 46,XX,del(12)(q14.2q15). arr cgh 12q14.2q15(rs10506536 rs10492198)x1 de novo for patient 3.

We conclude that we have identified a newly recognisable microdeletion syndrome involving chromosome 12q14. The clinical phenotype is mainly characterised by mild mental retardation, low birth weight with failure to thrive in early infancy and proportionate short stature. The osteopoikilosis lesions on skeletal radiographs are the most distinguishing feature of this microdeletion syndrome that should facilitate recognition of this peculiar disorder among children with mental retardation and growth failure.

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Authors' affiliations

Björn Menten, Karen Buysse, Jan Hellemans, Frank Speleman, Geert Mortier, Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium
Farah Zahir, Sara J Hamilton, Barbara C McGillivray, Marco A Marra, Jan M Friedman, Department of Medical Genetics, University of British Columbia, Vancouver, Canada
Teresa Costa, IWK Health Centre, Halifax, Nova Scotia, Canada
Carrie Fagerstrom, George Anadiotis, Daniel Kingsbury, Legacy Emanuel Children's Hospital, Portland, Oregon, USA

Correspondence to: Geert MortierMD, PhD, Department of Medical Genetics, Ghent University Hospital, De Pintelaan 185, B-9000 Gent, Belgium; geert.mortier@UGent.be

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