European Journal of Medical Genetics 56 (2013) 163–170

Contents lists available at SciVerse ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Chromosomal imbalance report

A novel microdeletion syndrome at 9q21.13 characterised by mental retardation, speech delay, epilepsy and characteristic facial features

Elise Boudry-Labis [a,*], Bénédicte Demeer [b], Cédric Le Caignec [c], Bertrand Isidor [c], Michèle Mathieu-Dramard [b], Ghislaine Plessis [d], Alice M. George [e], Juliet Taylor [f], Salim Aftimos [f], Adelheid Wiemer-Kruel [g], Jürgen Kohlhase [h], Göran Annerén [i], Helen Firth [j], Ingrid Simonic [j], Joris Vermeesch [k], Ann-Charlotte Thuresson [i], Henri Copin [l], Donald R. Love [e], Joris Andrieux [a]

[a] Institut de Génétique Médicale, Hôpital Jeanne de Flandre, CHRU de Lille, Avenue Eugène Avinée, 59037 Lille, France
[b] Service de Génétique Médicale, CHRU d'Amiens, France
[c] Service de Génétique Médicale, CHU Nantes, France
[d] Service de Génétique, CHU Clémenceau, Caen, France
[e] Diagnostic Genetics, LabPLUS, Auckland City Hospital, New Zealand
[f] Genetic Health Service New Zealand – Northern Hub, Auckland City Hospital, New Zealand
[g] Epilepsy Center, Kehl-Kork, Germany
[h] Center for Human Genetics, Freiburg, Germany
[i] Department of Immunology, Genetics and Pathology, ScilifeLab, Uppsala University, Uppsala, Sweden
[j] Dept of Medical Genetics, Box 134, Addenbrooke's Hospital, Cambridge, United Kingdom
[k] Center for Human Genetics, Katholieke Universiteit Leuven, Belgium
[l] Médecine et Biologie reproduction et cytogénétique, Centre de Gynécologie-Obstétrique, Université Picardie, CHU d'Amiens, France

ARTICLE INFO

Article history:
Received 7 August 2012
Accepted 17 December 2012
Available online 29 December 2012

Keywords:
9q21.13
Interstitial deletion
Mental retardation
Epilepsy
RORB
Array-CGH

ABSTRACT

The increased use of array-CGH and SNP-arrays for genetic diagnosis has led to the identification of new microdeletion/microduplication syndromes and enabled genotype–phenotype correlations to be made. In this study, nine patients with 9q21 deletions were investigated and compared with four previously Decipher reported patients.

Genotype–phenotype comparisons of 13 patients revealed several common major characteristics including significant developmental delay, epilepsy, neuro-behavioural disorders and recognizable facial features including hypertelorism, feature-less philtrum, and a thin upper lip. The molecular investigation identified deletions with different breakpoints and of variable lengths, but the 750 kb smallest overlapping deleted region includes four genes. Among these genes, *RORB* is a strong candidate for a neurological phenotype.

To our knowledge, this is the first published report of 9q21 microdeletions and our observations strongly suggest that these deletions are responsible for a new genetic syndrome characterised by mental retardation with speech delay, epilepsy, autistic behaviour and moderate facial dysmorphy.

1. Methods of detection

1.1. Cytogenetics

Chromosomal analysis of peripheral blood lymphocytes was performed according to routine procedures using RHG-banding (patient # 4 and # 5) or GTG-banding (patient # 1, 2, 3, 6, 7, 8) at approximately 550 band resolution per haploid set.

1.2. Array-CGH

1.2.1. Patients # 1–4

High resolution oligonucleotide array-CGH using a 44K array (patients # 1–3) or a 180K ISCA design array (patient #4) (Agilent™, Agilent Technologies, Santa Clara, Ca, USA) were performed following standard and manufacturer's recommendations. Female or male genomic DNAs (Agilent™) were used as sex-match references. Chromosome aberrations were analysed with the CGH analytics© software by applying an ADM-2 algorithm.

1.2.2. Patients # 5–9

As shown in Table 1, Agilent 105 K and 180 K, Affymetrix SNP6 and 2.7 M were also used following manufacturer's instructions.

* Corresponding author. Tel.: +33 0 320445616; fax: +33 0 320446804.
E-mail address: elise.labis@chru-lille.fr (E. Boudry-Labis).

1769-7212/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmg.2012.12.006

Table 1
Clinical findings in patients with 9q deletions encompassing the sub-band 9q21.13 [sMLPA: synthetic MLPA; ND: not done].

Patient ID	#1	#2	#3	#4
Decipher	250158	250165	254973	253847
Karyotype GTG/RHG	GTG 46,XY	GTG 46,XY,t(2; 9)(q32; q13)dn	GTG 46,XY,t(1; 16)(p13.3; q21)mat	RTG 46,XY
CGHa/SNPa	Agilent 44K	Agilent 44K	Agilent 44K	Agilent 180K ISCA design
Deletion size (Mb)	5.6–5.9	6.5–6.7	7.1–7.3	9.9
Boundaries (hg19)				
Non Deleted	73788472	73483203	72137166	73644450
Deleted	73920074	73588788	72182955	73661807
Deleted	79528971	80076668	79312306	83532389
Non Deleted	79671543	80144135	79403053	83576052
Method of validation	FISH	FISH	qPCR	FISH
de novo/inherited	dn	dn	Father non tested	dn
Age at diagnosis (years)	8	8	15	2
Sex	M	M	M	M
Birth	at term	at term		
Height (cm)	53.5		51	48
Weight (g)	3850	4330	3570	3090
HC (cm)	34.5		34	34.5
Apgar	10/10		10	
Mental retardation	Y	Y	Y	Y
Speech disorder/speech delay	Y	Y	Y	Y
Hypotonia	N	N		N
Developmental retardation	Y	Y	Y	Y
Epilepsy/Seizure	Y	N	Y	N
Autistic behaviour	Y	Y	Y	Y
Behavioural problems/Hyperactivity	ND	N	Y	Y
Brain MRI	Chiari type I		Normal	Normal
Height-weight delay	N	Y (H−2 SD W:0 SD)	Y (H−3 SD W:−2.5 SD)	Y (−2DS)
Facial dysmorphy	Y	Y	Y	Y
Ocular abnormalities	N	Strabismus		N
Cardiac abnormalities	N	N		N
Skeletal malformations	N	N		N
Hypertrichosis	Y	Y	N	N
Prenatal abnormalities:	N	N	N	Y Large umbilicus Nuchal translucency
Photography for publication	Y	Y	Y	Y

Patient ID	#5	#6	#7	#8
Decipher	250142	250392	261683	257363
Karyotype GTG/RHG	RTG 46,XY	GTG 46,XX	GTG 46,XY	GTG 46,XX
CGHa/SNPa	Affymetrix GeneChip 6.0 SNP	Agilent 105K	Agilent 180K	Affymetrix 2.7M
Deletion size (Mb)	2.2	11.0	2.2–2.3	6.8
Boundaries (hg19)				
Non Deleted	77046886	74374080	76998451	71021668
Deleted	77047469	74391472	77058421	71025196
Deleted	79291332	85348840	79277191	77807140
Non Deleted	79291813	85419612	79292629	77810520
Method of validation	FISH	qPCR	qPCR	Visible karyotype
de novo/inherited	dn	dn	dn	dn
Age at diagnosis (years)	12	6	16	15
Sex	M	F	M	F
Birth	At term	40 weeks	39 weeks	At term
Height (cm)		51	51	
Weight (g)	3320	3640	3000	3500
HC (cm)		34	33	
Apgar		10/10	10/10	8 and 10
Mental retardation	Y	Y	Y	Y
Speech disorder/speech delay		Y	Y	Y
Hypotonia	N	N	Y	Y
Developmental retardation	Y	Y	Y	Y
Epilepsy/Seizure	Y-photosensitive epilepsy	Y	Y	Y
Autistic behaviour	Y	Y	N	Y
Behavioural problems/Hyperactivity	Y	Y	N	N
Brain MRI	Slight hippocampal asymmetry	Corpus call. hypoplasia	Normal	Normal
Height-weight delay	N	N	Y	Y
Facial dysmorphy	Y	Y	N	Y
Ocular abnormalities	N	Y (hyperopia, strabismus)	N	N
Cardiac abnormalities	N	N	N	N
Skeletal malformations	N	N	N	Y
Hypertrichosis	N	Y	N	N
Prenatal abnormalities:	N	N	N	N
Photography for publication	Y	Y	Y	Y