Human Genetics (2019) 138:1145–1153
https://doi.org/10.1007/s00439-019-02048-y

ORIGINAL INVESTIGATION

The rare 13q33–q34 microdeletions: eight new patients and review of the literature

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Received: 16 April 2019 / Accepted: 12 July 2019 / Published online: 18 July 2019

Abstract

The objective of this study is to shed light on the phenotype and inheritance pattern of rare 13q33–q34 microdeletions. Appropriate cases were retrieved using local databases of two largest Israeli centers performing CMA analysis. In addition, literature search in PubMed, DECIPHER and ClinVar databases was performed. Local database search yielded eight new patients with 13q33.1–q34 microdeletions (three of which had additional copy number variants). Combined with 15 cases detected by literature search, an additional 23 cases were reported in DECIPHER database, and 17 cases from ClinVar, so overall 60 patients with isolated 13q33.1–q34 microdeletions were described. Developmental delay and/or intellectual disability were noted in the vast majority of affected individuals (81.7% = 49/60). Of the 23 deletions involving the 13q34 cytoband only, in 3 cases, developmental delay and/or intellectual disability was not reported. Interestingly, in two of these cases (66.7%), the deletions did not involve the terminal *CHAMP1* gene, as opposed to 3/20 (15%) of patients with 13q34 deletions and neurocognitive disability. Facial dysmorphism and microcephaly were reported in about half of the overall cases, convulsions were noted in one-fifth of the patients, while heart anomalies, short stature and hypotonia each involved about 10–30% of the cases. None of the 13q33–q34 deletions were inherited from a reported healthy parent. 13q33–q34 microdeletions are rare chromosomal aberrations, associated with high risk for neurodevelopmental disability. The rarity of this chromosomal aberration necessitates continuous reporting and collection of available evidence, to improve the ability to provide accurate genetic counseling, especially in the context of prenatal setting.

Introduction

Chromosomal microarray analysis (CMA) is considered a first-tier test for patients with developmental delay/intellectual disability, multiple congenital anomalies, and/or autism spectrum disorders (Manning and Hudgins 2010). In these symptomatic individuals, CMA technology has a diagnostic yield of 15–20%, compared to 3% with traditional karyotyping (Miller et al. 2010). This improved detection rate facilitates genetic diagnosis, prevents unnecessary diagnostic testing and allows a couple to opt for prenatal/preimplantation testing.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00439-019-02048-y) contains supplementary material, which is available to authorized users.

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Nevertheless, one of the most important problems of genetic tests with improved resolution is the detection of new previously undescribed or poorly described variants. Detection of findings for which there is limited data regarding the phenotypic spectrum may result in significant challenges in genetic counseling due to uncertainty of the phenotypic spectrum and the related penetrance. Counseling can be even more complicated in cases where a combination of several rare variants is detected, for example, as a result of an unbalanced translocation. Thus, the importance of describing rare CMA findings cannot be overemphasized.

Deletions of 13q33–q34 cytobands are rare chromosomal aberrations, associated with developmental delay and/or intellectual disability, facial dysmorphism, and an increased risk for epilepsy, cardiac defects and additional anatomic anomalies. Literature evidence describing the clinical characteristics is scarce (Kirchhoff et al. 2009; Huang et al. 2012; Yang et al. 2013; McMahon et al., 2015; Reinstein et al. 2016; Orsini et al. 2018). Thus, the objective of our manuscript was to shed light on the phenotype and inheritance pattern of this unique microdeletion.

Methods

Cases with deletions involving the 13q33.1–q34 cytoband were retrieved using several strategies:

1. Patient charts and lab reports of the two largest Israeli centers performing CMA analysis by one of the two platforms: CytoScan 750 K array (Thermo Fisher Scientific, Santa Clara, CA, USA) or Infinium OmniExpress-24 v1.2 BeadChip (Illumina Inc., San Diego, CA, USA), both using about 750,000 probes with an average resolution of 100 Kb).
2. Literature search in PubMed database for articles in English, describing the clinical phenotypes related to 13q33.1–q34 deletions. Articles not reporting exact genomic CMA coordinates of the variants were excluded.
3. DECIPHER database version 9.26 (Firth et al. 2009), using the coordinates of the largest involved deletion (case 5). We excluded patients with no reported phenotype, variants extending beyond the 13q33.1 band, and cases involving additional clinically significant (pathogenic or likely pathogenic) copy number variants.
4. ClinVar: public archive of interpretations of clinically relevant variants, looking for terminal 13q33–q34 deletions (including CHAMP1 gene, as detailed below), sized above 50 Kb.

Unless noted otherwise, genome map GRCh37/hg19 was used for all coordinates.

Prevalence of various phenotypic features was presented as numbers (percentages). As literature cases usually include more detailed clinical information compared to public databases, a separate analysis of clinical characteristics was performed in these two subgroups.

Results

Search details are presented in Fig. 1. Local database search yielded eight patients with 13q33.1–q34 deletion that have not been reported previously (Table 1). Of these, five cases were diagnosed with isolated microdeletions involving the 13q33.1–q34 cytoband, while three cases yielded 13q deletions combined with other chromosomal aberrations. Interestingly, we scanned our database of 5541 tests performed in

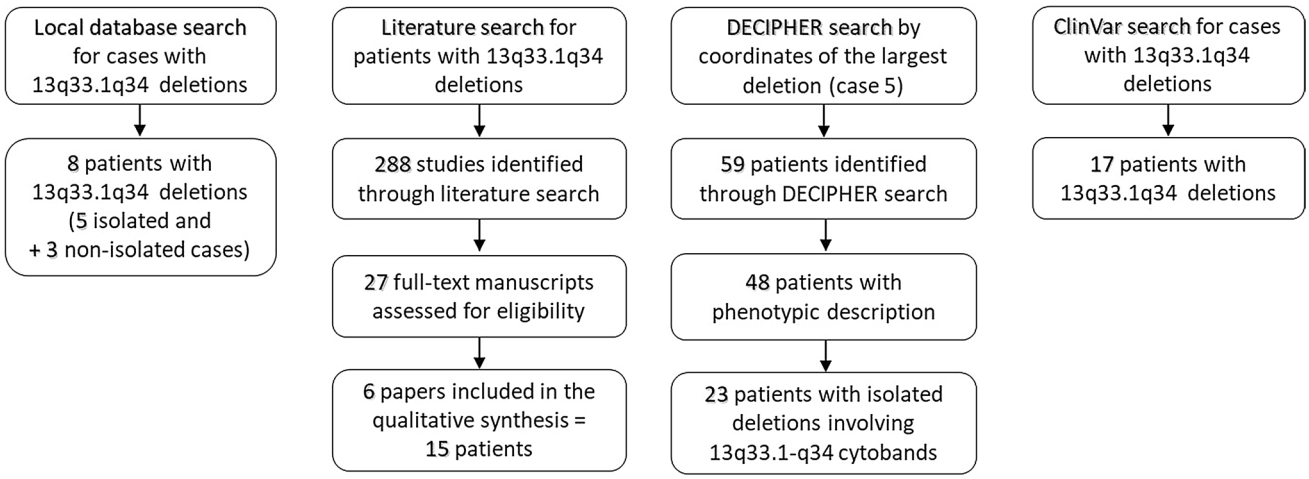

Fig. 1 Description of the search process for deletions involving 13q33–q34 cytoband

Table 1 Phenotypic characteristics and inheritance patterns of patients with 13q33–q34 deletions

	ISCN 2016	Size [Kb]	Age	Gender	Phenotype	Inheritance
Isolated partial 13q33–q34 deletions (new unpublished patients)						
1	arr[GRCh37] 13q34 (111780876_115107733)×1	3327	17 years	M	Developmental delay, microcephaly, speech apraxia, delayed puberty, gynecomastia, central obesity, fifth finger clinodactyly, lateral deviation of feet	Normal maternal karyotype, father not examined
2	arr[GRCh37] 13q33.3q34 (108791257_115169878)×1	6379	5 years	F	Developmental delay, microcephaly, hypermetropia, strabismus	De novo
3	arr[GRCh37] 13q33.2q34 (105321186_112327360)×1	7006	1 month	M	Oligohydramnion, IUGR (born 35 w 1425 g), developmental delay, microcephaly (below 2 pc), dysmorphism, bilateral ear canal atresia, severe failure to thrive, feeding difficulties (percutaneous gastrostomy insertion at the age of 3 months), recurrent urinary tract infections due to reflux, thoracolumbar scoliosis, hypotonia	NA
4	arr[GRCh37] 13q33.1q34 (104753418_115107733)×1	10,354	7 years	M	Intellectual disability (DQ 25), microcephaly, facial dysmorphism and asymmetry, prominent ears, torticollis, pectus excavatum, patent foramen ovale	De novo
5	arr[GRCh37] 13q33.1q34(101744044_115169878)×11	13,425	10 years	M	Developmental delay, intellectual disability (moderate), ataxia, dysarthria, microcephaly, dysmorphism (elongated facies, almond eyes, simple ears, long fingers), ambiguous genitalia, hypospadias, craniosynostosis, MRI—brain atrophy with delayed myelinization and thin corpus callosum.	De novo
Partial 13q33–q34 deletions combined with additional copy number variants (new unpublished patients)						
6	arr[GRCh37] 13q34 (111117691_115107733)×1 arr[GRCh37] 9p24.3p24.1 (208,454_7,709,519)×13	3990	32 years	F	Intellectual disability, cleft palate, hypotonia, strabismus, scoliosis, obesity, abnormal palmar creases, hypoplasia/aplasia fifth right finger phalanx, bilateral feet brachydactyly	De novo
7	arr[GRCh37] 13q34 (112092656_115169878) arr[GRCh37] arr17q25.2q25.3 (74940769_81195210)×13	3077	6 years	F	Intellectual disability, heart defect (not specified), polydactyly, dysmorphism	NA
8	arr[GRCh37]13q33.3q34 (109149281_115107733)×1 arr [GRCh37] 18q23 (75135849_78013728)×1	5958	2 years	M	Developmental delay (DQ 61), postnatal microcephaly, hypotonia, facial dysmorphism (sloping forehead, mild synophris, epicanthus with mild blepharophimosis, long eyelashes, periorbital swelling, low and wide nasal bridge, flat philtrum, prominent upper lip, retrognatia, full chicks with prominent nasolabial folds, long earlobes), recurrent upper respiratory tract infections	De novo

F female, *m* male, *ISCN* International System for Human Cytogenomic Nomenclature, *NA* non-accessible

low-risk pregnancies and did not detect similar copy number variants (Sagi-Dain et al. 2019).

Literature search yielded 6 papers that provided data regarding additional 15 patients with isolated 13q33.1–q34 deletions, with available genomic coordinates (Kirchhoff et al. 2009; Huang et al. 2012; Yang et al. 2013; McMahon et al. 2015; Reinstein et al. 2016; Orsini et al. 2018). A detailed description of phenotypic characteristics, inheritance patterns and involved genes of cases retrieved

from local database and literature search is presented in Tables 1, 2.

DECIPHER search using the coordinates of the largest deletion (case 5) revealed 59 patients. Of these, 11 were excluded due to the lack of phenotypic characterization, 19 due to involvement of additional copy number variants, and additional 6 due to deletions that extended beyond the 13q33.1 band (Supplementary Table 1). Of the 23 relevant cases, sized from 1.14 to 12.77 Mb, 20 were diagnosed with developmental delay/intellectual disability. In 10 cases, the parents were not tested, in 11 patients the deletion occurred de novo, while 2 deletions (sized 3.74 Mb and 6.68 Mb) were maternally inherited; however, in the latter cases, no information regarding the maternal health and mental status was noted.

ClinVar database search yielded 17 additional terminal 13q33–q34 deletions (Supplementary Table 2).

A summary of the phenotypic features of the 60 patients is presented in Table 3. Developmental delay and/or intellectual disability were noted in the vast majority of affected individuals (81.7). Of the 23 deletions involving the 13q34 cytoband only, in 3 cases developmental delay and/or intellectual disability was not reported. Interestingly, in 2 of these cases (66.7%), the deletions did not involve the terminal *CHAMP1* gene, as opposed to 3/20 (15.0%) of patients with 13q34 deletions and neurocognitive disability (Fig. 2, Supplementary Table 3).

Overall, of the 32 cases with known inheritance, 25 (78.1%) were de novo, 5 were inherited from an affected parent, and 2 were inherited from a parent for which no clinical data were reported. None of the 13q33.1–q34 deletions was inherited from a reported healthy parent.

Discussion

Data reported in the literature describing the clinical characteristics of submicroscopic terminal deletions of the long arm of chromosome 13 are scarce. The first report of 13q deletion in patients with mental and growth retardation was published in 1963 (Lele et al. 1963), and the deletion was named as a distinct syndrome in 1969 (Allderdice et al. 1969). Studies published in the era of traditional karyotyping described a wide spectrum of symptoms and signs, including moderate to severe intellectual disability, failure to thrive, microcephaly, brain malformations including Dandy–Walker and holoprosencephaly, digital anomalies, intestinal defects, and anogenital malformations (Tranebjaerg et al. 1988; Brown et al. 1993; Christofolini et al. 2006).

In 2007, Ballarati et al. published the first comprehensive molecular characterization of 14 patients carrying partial de novo 13q deletions (Ballarati et al. 2007). The deleted segments ranged from terminal 13q34–qter loss sized 4.2–75.7 Mb deletion of q13.3–qter. As 13q32 was previously defined as the critical band for severe phenotypes, including brain malformations (Brown et al. 1995), the 13q deletions were grouped according to the inclusion or exclusion of the 13q32 band (group 1—proximal to q32, group 2—including q32, group 3—distal to q32). Two patients were diagnosed with group 3 deletions (13q33.3–qter and 13q34–qter(, both presenting with moderate intellectual disability, intra-uterine growth restriction and microcephaly, but no major malformations.

In 2009, Quelin et al. described 12 patients with 13q deletions (9 fetuses and 3 children) (Quelin et al. 2009). The cohort included two female patients aged 14 and 13 years old, with 13q deletions sized 5.5 Mb and 11 Mb (encompassing 13q33.3–qter and 13q33.1–qter, respectively). Both presented with intra-uterine growth restriction, short stature and intellectual disability, while the patient with the larger deletion was characterized by microcephaly and aortic coarctation.

In 2009, Kirchhoff et al. described clinical and molecular data of additional 14 individuals with de novo 13q deletions (Kirchhoff et al. 2009). Of these, five deletions involved "group 3" regions relevant to our study (Table 1), presenting with rather common characteristics including moderate to severe intellectual disability, microcephaly, hypotonia, and facial dysmorphism (such as prominent columella with short philtrum). The authors defined the terminal 6 Mb region of 13q as a "microcephaly-critical region", and suggested several candidate genes, mainly *ARHGEF7* (OMIM #605477, involved in human cerebral cortex development), *UPF3B* (OMIM #300298, associated with intellectual disability), and *SOX1* (OMIM #602148, linked to neuronal differentiation).

In 2012, a group from Department of Cardiothoracic Surgery performed single-nucleotide polymorphism array in individuals with syndromic congenital heart defects, and detected a large group 3 deletion (13q33.1–qter) in a 1-year-old female patient with intra-uterine growth restriction, ventricular septal defect, arterial septal defect and cor triatriatum, mild facial dysmorphism, short stature and intellectual disability (Huang et al. 2012). In addition, extended prothrombin time was noted, with Factor X and VII levels 75% and 49% of normal levels, respectively. The authors reviewed previous reports of 10 patients with 13q deletions and heart defects, and suggested that the critical region for cardiac anomalies lies within the distal 6 Mb. In 2013, the same group presented an additional patient with a heart defect (a single atrium), mild intellectual disability, and polydactyly, associated with the smallest reported distal 13q deletion, sized slightly above 1 Mb (Yang et al. 2013). The single OMIM morbid gene in the region, GRK1, associated with a rare autosomal recessive Oguchi disease type 2 characterized by stationary night blindness, could not explain the

Table 2 Additional publications describing isolated partial 13q33–q34 deletions

	ISCN 2016	Size [Kb]	Age	Gender	Phenotype	Inheritance
Kirchhoff et al. (2009)	arr[GRCh37] 13q33.3q34 (108193520_ter)×11	6976	2 years and 5 months	M	Moderate intellectual disability, microcephaly, hypotonia, dysmorphism	De novo
	arr[GRCh37] 13q33.3q34 (107044937_ter)×1	8124	18 years	M	Severe intellectual disability, microcephaly, short stature, hypotonia, seizures, dysmorphism	De novo
	arr[GRCh37] 13q33.3q34 (106768340_ter)×1	8401	13 years	F	Severe intellectual disability, microcephaly, short stature, hypotonia, dysmorphism	De novo
	arr[GRCh37] 13q33.2q34 (105108929_ter)×1	10,060	10 years	F	Moderate intellectual disability, microcephaly, hypotonia, dysmorphism	De novo
	arr[GRCh37] 13q33.1q34 (103107018_ter)×1	12,062	3 years and 4 months	F	Moderate intellectual disability, microcephaly, hypotonia, seizures, dysmorphism, PV stenosis	De novo
Huang et al. (2012)	arr[GRCh36] 13q33.1q34 (101379024_114127095)×1	12,748	1 year	F	Developmental delay, IUGR and FTT (HC not mentioned), VSD and ASD, facial dysmorphism, decreased factor X and VII levels	De novo
Yang et al. (2013)	arr[GRCh37] 13q34 (113987623_115107157)×1	1119	13 years	M	Mild intellectual disability, HC not mentioned, single atrium, polydactyly	De novo
McMahon et al. (2015)	arr[GRCh37] 13q33.3q34 (108570480_111106213)×1	2535	6 years	M	Developmental delay, microcephaly, mild facial dysmorphism, complex cardiac malformation[a]	De novo
Reinstein et al. (2016)	arr[GRCh38] 13q34 (110647373_114344403)×1	4197	35 years	F	Developmental delay, mild intellectual disability, microcephaly, VSD, mild facial dysmorphism	De novo
	arr[GRCh38] 13q34 (111523966_114344403)×1	2820	24 (F), 28 (F), 32 (M), 57 (F)		Developmental delay, microcephaly (2/4), mild facial dysmorphism, epilepsy (1/4)	Three inherited from affected parent
Orsini et al. (2018)	arr[GRCh37] 13q34 (111511614_112873904)×1	1362	7 (M), 1.5 (M)		Developmental delay, mild intellectual disability, microcephaly, epilepsy, dysmorphism, short stature	Inherited from affected parent

ISCN International System for Human Cytogenomic Nomenclature

[a]Double outlet right ventricle (DORV), anterior aorta, multiple ventricular septal defects, pulmonary stenosis

Table 3 Clinical findings in individuals with isolated 13q33–q34 deletions

	Cases described in the literature				Open access databases cases				Overall ($n=60$)	
	The current article ($n=5$)	Previously published cases ($n=15$)	Overall ($n=20$)		DECIPHER ($n=23$)	ClinVar ($n=17$)	Overall ($n=40$)			
			n	%			*n*	%	*n*	%
ID/DD	5	15	20	100.0	20	9	29	72.5	49	81.7
ID	2	9	11	55.0	14	1	15	37.5	26	43.3
DD	4	9	13	65.0	9	9	18	45.0	31	51.7
Dysmorphism	3	14	17	85.0	7	2	9	22.5	26	43.3
Microcephaly	5	11	16	80.0	6	2	8	20.0	24	60.0
Convulsions	0	5	5	25.0	3	3	6	15.0	11	18.3
Heart anomalies	1	5	6	30.0	0	1	1	2.5	7	11.7
Hypotonia	1	5	6	30.0	1	0	1	2.5	7	11.7
Short stature	1	5	6	30.0	1	1	2	5.0	8	13.3
Genitourinary malformations	1	0	1	5.0	2	3	5	12.5	6	10.0

DD developmental delay, *ID* Intellectual disability

phenotype. Further extension of the cardiac involvement was added by McMahon et al., describing a patient with an interstitial 2.5 Mb 13q33.3q34 deletion, presenting with double outlet right ventricle, anterior aorta, multiple ventricular septal defects, pulmonary stenosis, in addition to developmental delay and microcephaly (McMahon et al. 2015).

In 2016 Reinstein et al. described two additional families, including the first report of 2.8 Mb 13q34 deletion inherited from an affected mother (Reinstein et al. 2016). Finally, in 2018 Orsini et al. published another report of a 13q34 deletion inherited from an affected parent (Orsini et al. 2018).

In our report, we present eight new patients with 13q33–q34 microdeletions, three of which were with additional chromosomal aberrations. Integration of the clinical characteristics of isolated 13q33–q34 deletions reported in our manuscript, along with data from previously published literature, enables to conclude that developmental delay and/or intellectual disability are universal features observed in the vast majority of affected individuals. Facial dysmorphism and microcephaly were reported in about half of the cases, convulsions were noted in one-fifth of the cases, while heart anomalies, short stature and hypotonia involved about 10–30% each. None of the 13q33–q34 deletions was inherited from a healthy parent, and no reports describing the presence of such deletions in normal individuals were found.

The 13q33–q34 locus contains over 130 genes, 36 of these were OMIM morbid. According to DECIPHER database (Firth et al. 2009), only four genes were noted as low haploinsufficiency score, i.e., more likely to not exhibit haploinsufficiency (%HI 90–100)—*DAOA* (OMIM #607408, associated with schizophrenia), *CCDC168*, *TEX29* and *SPACA7* (not associated with known disorders in human). All four were annotated with a low probability of loss of function (LoF) intolerance (low pLi). Fourteen genes were annotated with high pLi (> 0.9), of these only two were associated with medical conditions in humans—*COL4A1* and CHAMP1.

According to UCSC database (https://genome.ucsc.edu/), five of the genes contained in the 13q33–q34 locus are associated with possibly relevant autosomal dominant disorders (Supplementary Table 4). The genes *COL4A1* (OMIM 120130) and *COL4A2* (OMIM 120090) are related to porencephaly and/or schizencephaly, as well as vascular anomalies. Mutations in *FGF14* (OMIM #601515) are related to spinocerebellar ataxia type 27, while the proximal *NALCN* gene (OMIM #611549) is associated with autosomal dominant disorder of congenital limb and face contractures, hypotonia, and developmental delay (MIM #616266).

Very rare deletions and truncating mutations in the terminal *CHAMP1* gene (OMIM #616579) have been associated with type 4 autosomal dominant mental retardation syndrome. According to gnomAD browser (http://gnomad.broadinstitute.org/), the expected frequency of LoF mutations in CHAMP1 gene is 23.8; however, only 2 individuals were found in a population encompassing 141,456 healthy cases, hence the pLi of 0.99. Similar pLi was yielded in the ExAC database (http://exac.broadinstitute.org/), since no LoF mutations in *CHAMP1* gene were found in a healthy population totaling 60,706 cases, as opposed to an expected frequency of 12.5. As previously described, the terminal *CHAMP1* gene was not involved in two of the three 13q34 deletions with no neurodevelopmental disability, as opposed to 3/17 (17.6%) of patients with 13q34 deletions and neurocognitive disorders. Thus, inclusion of *CHAMP1* gene in the deleted region might be associated with severity of neurocognitive delay, and might be related to the gene function or to its telomeric location, possibly involved in epigenetic mechanisms

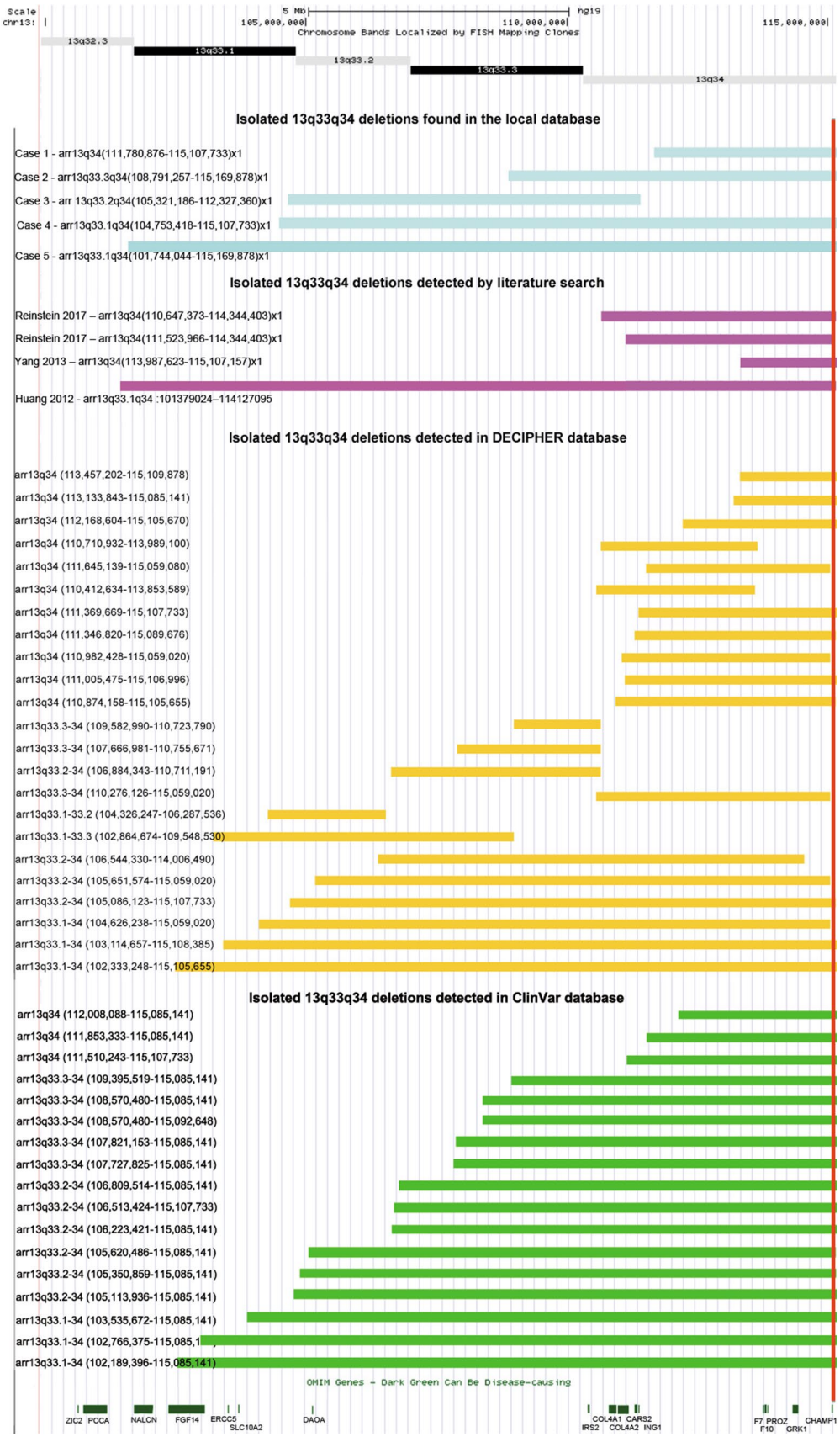

Fig. 2 13q33.1—q34 cytoband deletions presented in our study and detected by literature search (location of *CHAMP1* gene is marked by the red band)

affecting the stability of the locus. However, inferring a relationship between CHAMP1 and intellectual disability from the three patients with 13q34 deletions not involving CHAMP1 in DECIPHER might not be valid, as two of them were 1 year (ID 275984) or even less than 1 year old (ID 304478) at the time of recording, and the third one's age is unknown (ID 249531).

The majority (25/32, 78%) of 13q33–q34 deletions described in our manuscript were de novo, while seven were inherited from affected parents (Firth et al. 2009; Reinstein et al. 2016; Orsini et al. 2018). The clinical penetrance seems to be high, as no unaffected individuals with distal 13q deletions were reported. An important finding is that the microdeletion was not detected in a large cohort of 5541 CMA results in pregnancies with normal ultrasound (representing healthy population) (Sagi-Dain et al. 2019). Also, in cases of additional chromosomal anomalies, the phenotype is even more difficult to predict, which further aggravates the complexity of the genetic counseling. However, it seems that combined cases bear even higher risk for intellectual disability (cases 6–8 in Table 1, and 19 more cases that were excluded in the Decipher database).

In summary, 13q33–q34 deletions are rare chromosomal aberrations, associated with developmental delay and/or intellectual disability, facial dysmorphism, and an increased risk for epilepsy, cardiac defects and additional anatomic anomalies. In our report, we present eight new patients with terminal 13q33–q34 microdeletions, including some of the smallest copy number variants reported at this locus. Further evidence including functional information will most probably be revealed in the coming years, including the specific effects of each gene encompassed by the segment, with an emphasis on the effects of *CHAMP1* gene on phenotypic expression of patients with such 13q33–q34 microdeletions. The rarity of this aberration necessitates continuous reporting and collection of available evidence to facilitate the accuracy of genetic counseling that is especially important in the prenatal setting.

Author contribution LS-D and IM contributed to conception and design, analysis and interpretation of data and drafting the article. YG, AP, RS-H, ES-D, ZA, BYSJ, SB-S, CV and LB-S contributed to data collection, revising the article, providing intellectual content of critical importance to the work described and final approval of the version to be published.

Funding None.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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