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# Terminal microdeletions of 13q34 chromosome region in patients with intellectual disability: Delineation of an emerging new microdeletion syndrome

Eyal Reinstein [a,b,*], Meytal Liberman [a], Michal Feingold-Zadok [c,1], Tamar Tenne [a], John M. Graham Jr. [d]

[a] Medical Genetics Institute, Meir Medical Center, Israel
[b] Sackler School of Medicine, Tel Aviv University, Israel
[c] Recanati Genetic Institute, Rabin Medical Center, Petah Tiqwa, Israel
[d] Dept. of Pediatrics, Cedars Sinai Medical Center, Harbor-UCLA Medical Center, University of California, Los Angeles, CA, USA

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ABSTRACT

The increasing use of chromosomal microarray studies in patients with intellectual disability has led to the description of new microdeletion and microduplication syndromes. We report terminal microdeletions in 13q34 chromosome region in 5 adult patients of two unrelated families. Patients harboring 13q34 microdeletions display common clinical features, including intellectual disability, obesity, and mild facial dysmorphism. These individuals can become fairly self-sufficient, however they do not live independently, and require community and social support. Further systematic analysis of the genes comprised in the deleted region will allow the identification of genes whose haploinsufficiency is expected to lead to disease manifestations, in particular intellectual disability.



## 1. Introduction

The increasing use of chromosomal microarray studies in patients with intellectual disability (ID) has led to the description of new microdeletion and microduplication syndromes. The identification of novel microdeletion and microduplication syndromes is based on consistent, clinically recognizable features associated with Copy Number Variations (CNVs) in common chromosomal regions. Because of the variability in expression and penetrance of clinical manifestations, the establishment of the clinical significance of many of the newly identified CNVs is complex [1].

Here we report five adult individuals of two unrelated families with similar ID syndrome bearing ~3 MB overlapping terminal microdeletions in chromosome region 13q34. We propose that terminal microdeletions in 13q34 cause a developmental disorder and possibly a recognizable phenotype.

## 2. Patients and methods

### 2.1. Family 1

The proband is a 35-year-old Jewish female of Iraqi/Afghani origin, the second child of healthy non-consanguineous parents. She was born at term at 2500 g for weight and had a single hospital admission at age 1 month because of pneumonia, with no additional hospitalizations since then. A ventricular septal defect (VSD) was diagnosed during infancy and she was followed since then with no associated complications. She had normal tonus and no feeding difficulties, yet all developmental milestones, motor, language and cognitive, were delayed. She was evaluated several times and found to have mild ID. There were neither sleeping problems nor seizures; vision and hearing are intact. She completed 12 years in special education institutes. Typical to individuals with mild ID, she is a rather fluent reader but has significant reading and spelling problems and severe mathematical difficulties [2]. She is currently working in bag packing at a local supermarket. Her mother is 62 and is healthy; she works as a schoolteacher and also has an isolated VSD. Her father is 65, works as an engineer, and healthy. She has two additional sisters with no medical problems. Physical examination revealed an overweight female (height 166 cm, weight 73 kg, BMI 26) with microcephaly (OFC 51 cm, <2 percentile) and mild facial dysmorphism including prominent nose with long nasal bridge and a

* Corresponding author at: Medical Genetics Institute, Meir Medical Center, Kfar-Saba, Israel.
*E-mail addresses:* Reinstein.eyal@gmail.com, eyalre1@clalit.org.il (E. Reinstein).
[1] Current affiliation: Genetic Institute, Assaf Harofe Medical Center, Zerifin, Israel.

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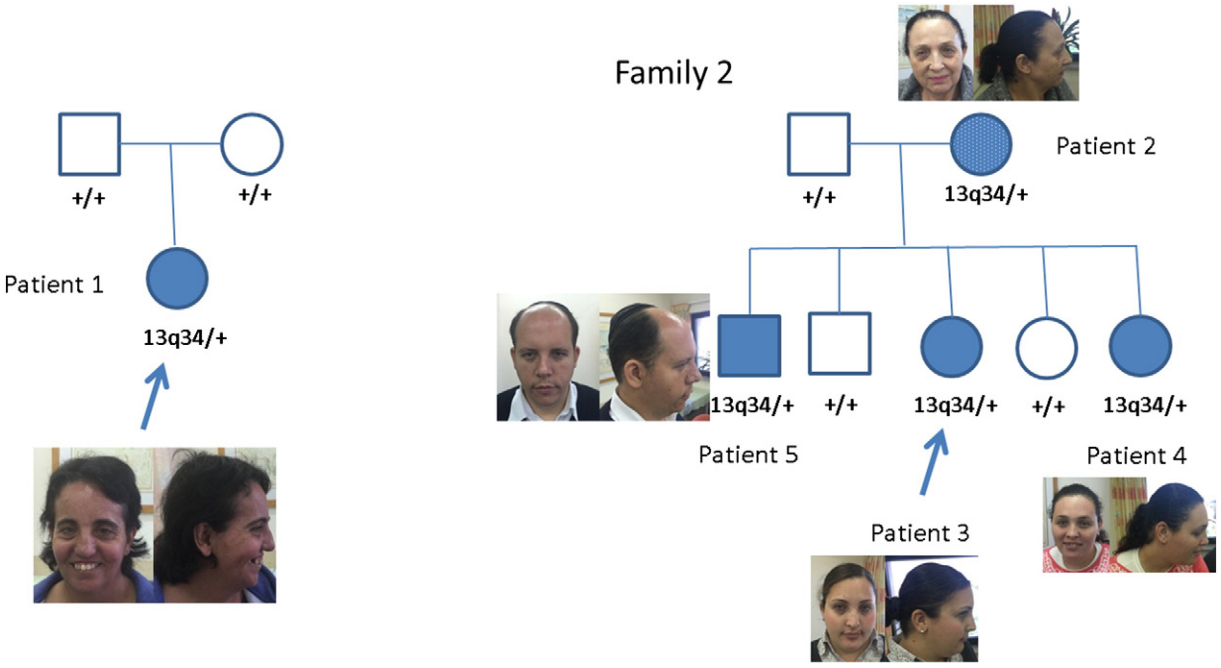


**Fig. 1.** Clinical features of patients with 13q34 microdeletion syndrome Pedigrees of families showing facial features and segregation of *13q34* terminal microdeletion. Wild-type 13q34 region is indicated by plus sign. Filled symbols indicate affected individuals. Filled symbols with white dots indicate affected individual with mosaic 13q34 microdeletion.

broad tip, a wide, rectangular forehead, small chin, down-slanting palpebral fissures, and mild ptosis (Fig. 1). Genetic studies including blood karyotype and fragile X analysis were normal. Chromosomal microarray study was performed using Illumina HumanOmniExpress-24 v1.0 beadchip technology and demonstrated a terminal microdeletion of 3.87 MB in chromosome region 13q34 (chr13: 110647373-114344403; GRCh38/hg38). Though both parents are academics and report neither developmental nor medical problems, to assess whether this is a reduced penetrant inherited microdeletion, Fluorescence *in situ* hybridization (FISH) assay was performed on parental samples using specific probes. The results showed no evidence of deletion or translocation, confirming *de novo* occurrence of the microdeletion in the proband.

### 2.2. Family 2

The proband is a 24-year-old female with ID that was referred for risk evaluation since her sister is pregnant. She is the fourth child of non-consanguineous Jewish Moroccan parents. She was born at term at 4000 g for weight and other than gastro–esophageal reflux, had no hospitalizations or medical complications. She had normal tonus and no feeding difficulties, however all developmental milestones, motor and cognitive, were delayed. She attended special education schools and was a resident of a foster home since age 4. Her expressive and receptive communication skills are developed and allow for her to convey to others her wishes and feelings. She is rather independent at home and takes part in the house duties and chores. She has not developed everyday basic math skills, and thus does not understand value of money and cannot shop independently. She can read and write at a basic level but has limited reading comprehension and low understanding of event sequence and her general IQ is 70. Hearing and vision are intact. She is currently working in a factory that employs individuals with special needs. She has three first degree family members with the same medical condition (Fig. 1 right panel). Her mother is 57 and was diagnosed with mild cognitive delay with low expressive language abilities, her 28 year old sister has mild ID and epilepsy, and her 32 year-old brother has mild ID. Her affected sister has a normal neurological exam, and normal CT and MRI of the brain. Her affected brother was born at term and had delayed developmental milestones. He attended special education schools, and does not have additional medical problems. He lives in a hostel for individuals with special needs. Her father, and two additional siblings, age 22 and 29, have no medical or neuro-cognitive problems. Physical examination showed overweight female (height 175 cm, weight 123 kg, BMI 40) with normocephaly (OFC 54 cm, 40 percentile) and mild facial dysmorphism. Her affected mother, sister and brother have rather similar facial features (Fig. 1), obesity, and microcephaly (sister OFC 52 cm, 2 percentile; brother; OFC 56 cm, 50 percentile and mother OFC 52.5 cm, ~2 percentile). In unaffected siblings, BMI's are within normal range and facial features show no dysmorphism.

Chromosomal microarray study performed on the proband's DNA sample demonstrated a terminal microdeletion of 3 MB in chromosome region 13q34 (chr13: 111523866-114344403; GRCh38/hg38). FISH assay using specific probes was completed on all first degree relatives and showed that her two affected siblings carry 13q34 microdeletions while her mother is mosaic for the microdeletion (241/304 abnormal cells; ~80% mosaicism).

## 3. Discussion

We report the phenotype associated with 13q34 terminal microdeletions in five adult individuals. In the first family, the microdeletion was a *de novo* event whereas in the second, it was inherited from an affected mother in whom the deletion was a result of a post-zygotic event leading to mosaicism. Affected individuals present in childhood with gross developmental delay and a comparable phenotype consisting of mild ID, obesity and mild dysmorphic facial features. We suggest that the variability of clinical expression is low and penetrance is complete in this microdeletion syndrome. Subjects harboring 13q34 terminal microdeletion can become fairly self-sufficient, however they do not live independently, and need community and social support. Furthermore, they do not seem to have additional medical manifestations during teenage and adult years. Though we hypothesize that the phenotype of affected patients is rather similar, it is unclear