A new 1p36.13-1p36.12 microdeletion syndrome characterized by learning disability, behavioral abnormalities, and ptosis

Aagaard Nolting, Line; Brasch-Andersen, Charlotte; Cox, Helen; Kanani, Farah; Parker, Michael; Fry, Andrew E.; Loddo, Sara; Novelli, Antonio; Dentici, Maria Lisa; Joss, Shelagh; Jørgensen, Joan P.; Fagerberg, Christina R.

Published in:
Clinical Genetics

DOI:
10.1111/cge.13739

Publication date:
2020

Document version:
Accepted manuscript

Citation for published version (APA):

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use
This work is brought to you by the University of Southern Denmark. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk

Download date: 15. Sep. 2023
A new 1p36.13-1p36.12 microdeletion syndrome characterized by learning disability, behavioral abnormalities, and ptosis

Short running title: 1p36.13-1p36.12 deletion syndrome

Line Nolting¹, Charlotte Brasch-Andersen¹, Helen Cox², Farah Kanani³, Michael Parker³, Andrew E. Fry⁴, Sara Loddo⁵, Antonio Novelli⁵, Maria Lisa Dentici⁶, Joss Shelagh⁷, Joan P. Jørgensen⁸, Christina R. Fagerberg¹

Affiliations

¹ Department of Clinical Genetics, Odense University Hospital, Odense, Denmark.
² West Midlands Regional Clinical Genetics Unit Birmingham U.K, Birmingham, United Kingdom.
³ Sheffield Clinical Genetics Service, Northern General Hospital, Sheffield, United Kingdom.
⁴ Institute of Medical Genetics, University Hospital of Wales, Heath Park, Cardiff, United Kingdom.
⁵ Laboratory of Medical Genetics, Bambino Gesù Childrens' Hospital, Rome, Italy.
⁶ Medical Genetics Unit, Bambino Gesù Children's Hospital, Rome, Italy.
⁷ Clinical Genetics, West of Scotland Genetic Services, the Queen Elisabeth University Hospital, Glasgow, United Kingdom.
⁸ Hans Christian Andersen Children’s Hospital, Odense University Hospital, Odense, Denmark

Corresponding author

Christina Ringmann Fagerberg, christina.fagerberg@rsyd.dk

Acknowledgements

We thank the patients and their families for their kind participation. This study makes use of data generated by the DECIPHER community. A full list of centres who contributed to the generation of
the data is available from http://decipher.sanger.ac.uk and via email from decipher@sanger.ac.uk. Funding for the project was provided by the Wellcome Trust.

Conflict of interest

The authors declare no conflicts of interest.

Data Available Statement

Not relevant. Most deletions can be seen in Decipher.

Abstract

Two 1p36 contiguous gene deletion syndromes are known so far: the terminal 1p36 deletion syndrome, and a 1p36 deletion syndrome with a critical region located more proximal at 1p36.23-1p36.22. We present even more proximally located overlapping deletions from seven individuals, with the smallest region of overlap comprising 1 Mb at 1p36.13-1p36.12 (chr1:19077793-20081292 (GRCh37/hg19)) defining a new contiguous gene deletion syndrome. The characteristic features of this new syndrome are learning disability or mild intellectual disability, speech delay, behavioral abnormalities, and ptosis. The genes *UBR4* and *CAPZB* are considered the most likely candidate genes for the features of this new syndrome.

Keywords

Chromosomes, Human, Pair 1; Ptosis; Chromosome Deletion; Learning disability; Behavioral abnormality

Introduction

1p36 terminal deletion is considered the most common terminal deletion in humans with an incidence of 1 in 5000 newborns.\(^1\)\(^-\)\(^3\) Partial monosomy of chromosome 1p36 was first described in 1980, and in 1997 Shapira et al. delineated the 1p36 deletion syndrome.\(^4\) The phenotype is variable with the most common features being intellectual disability, hypotonia, craniofacial dysmorphic features, growth delay, eye/vision problems, seizures and hearing impairment.\(^4\) Wu et al (1999) found the critical region to be of 6.29 Mb at 1p36.33-1p36.31 (chr1:1-6289973).\(^5\) In 2007 Kang et al defined a more proximal distinct 1p36 deletion syndrome with a critical region of 2.24 Mb at 1p36.23-1p36.22 (chr1:9124551-11362893) in five patients.\(^6\) The features linked to this region were cognitive deficits,
congenital malformations, hirsutism, frontal and parietal bossing, epicanthic folds, and broad and arched eyebrows. We present seven individuals from five families with even more proximally located overlapping interstitial deletions in 1p36.13-1p36.12 and define this as a third contiguous gene deletion syndrome linked to 1p36.

Material and methods
Cases with overlapping deletions in 1p36 were identified via the DECIPHER Database (Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources). Only individuals with isolated deletions less than 5 Mb were included in the study. The literature was reviewed to identify individuals with isolated overlapping 1p36 deletions.

Consent for publication of clinical features and photos were obtained from all individuals shown in figure 1.

Candidate genes in the smallest region of overlap (SRO) were selected as OMIM genes with a pLI score > 0.8 (pLI = probability of LoF intolerance) in the Genome Aggregation database (GnomAD, accession date July 2nd, 2019).

Results
Clinical features are listed in Table 1, and a summary of clinical features can be seen in Table 2. Detailed case descriptions can be seen in supplementary material.

Photos and schematic presentation of the 1p36 deletions are shown in Figure 1.

The SRO for individuals presenting with learning disability or mild intellectual disability, behavioral anomalies, and ptosis encompassed 1 Mb at chr1:19077793-20081292 (GRCh37/hg19). Individual 8 was described as non-dysmorphic and had a limited overlap with the SRO of 66 bp. She was not considered having the new microdeletion syndrome and her presence might indicate that the SRO could be even smaller.

The father of individual 3 was not available for analysis, and the mother did not have the deletion. The array data of individual 3 revealed 35 SNPs in the region of the deletion. Nine of 35 SNPs were not maternally inherited, and the deletion was concluded to be of the maternal allele. The remaining SNPs were non-informative but in concordance with loss of maternal allele. As the mother did not have the deletion, we conclude, that the deletion arose de novo in individual 3. The inheritance was thus known in all seven individuals.

Discussion

Skriv her
We present seven individuals with overlapping deletions in 1p36.13-1p36.12 and define a new microdeletion syndrome in 1p36 located more proximal to those previously described.

Four individuals were females, three were males. Five deletions occurred de novo (71%) while two siblings had inherited the deletion from their mother (29%). The majority was born at term and had a birth weight in the lower normal range. Postnatal growth was normal for all except one. Learning disability or mild intellectual disability was present in all except one who had moderate intellectual disability. Motor problems, behavioral anomalies and speech delay were seen in most individuals. Behavioral anomalies were seen in 57% (4/7), two of whom were diagnosed with ADHD. Dysmorphic features seen in at least 50% were congenital ptosis, pointed chin, high palate, misalignment of teeth, and epicanthus. Ophthalmologic features were seen in all (7/7), of which congenital ptosis – unilateral or bilateral – was the most distinct finding seen in 5/7 individuals (71%). Less frequent were hypermetropia, epicanthus, deep-set eyes, and heavy eyebrows. Mild hearing loss was seen in one individual. Present in 50% or less were congenital heart defect (ASD and/or VSD, pulmonary valve dysplasia), and features of hands and feet such as clinodactyly, syndactyly, camptodactyly, and arachnodactyly.

Congenital ptosis is a distinct feature seen in more than half of the individuals. Ptosis is defined as the upper eyelid being positioned lower than normal, thereby narrowing the palpebral fissures vertical axis. Ptosis is considered congenital, when present before one year of age. Congenital ptosis can result in abnormal visual function and development, such as amblyopia. The levator palpebra superior muscle which elevates the upper eyelid is innervated by the 3rd cranial nerve, n. oculomotorius. The pathophysiologic process leading to ptosis can be either neurogenic, myogenic, aponeurotic or mechanical. Congenital ptosis can occur isolated or as part of a syndrome. Congenital isolated ptosis most often occurs sporadically but can also be familial, and several loci and candidate genes have been suggested, including 1p32-1p34.1, Xq24–27.1, and the ZFH4 gene at 8q21.1. Congenital ptosis can be part of numerous genetic syndromes, some examples are congenital fibrosis of the extraocular muscles (KIF21A, PHOX2A, TUBB3), SIX2 haploinsufficiency, various types of myopathy, neurogenetic diseases, and mitochondrial diseases. The 1p36.13-1p36.12 microdeletion syndrome presented here is a new syndrome with ptosis as a distinct feature. Haploinsufficiency of one or more genes in this region is suspected to cause ptosis, but the relevant gene(s) and pathophysiological process are unknown.

The smallest region of overlap (SRO) encompasses 1 Mb at chr1:19077793-20081292. The SRO contains several genes, none of which are currently known to be haploinsufficient. The following genes, being the only ones with a pLI-score above 0.8, are suggested as possible candidate genes for features of this new microdeletion syndrome:

The UBR4 gene (OMIM 609890), encodes a mammalian N-recognin. The protein is present in all tissues but highly expressed in nervous tissue, where it is involved in neurogenesis and neuronal migration, and seems to have pro-survival roles in neurons. UBR4 deficient mice die during midgestation with multiple developmental anomalies. In humans UBR4 has been suggested to be a
modifier for episodic ataxia\textsuperscript{20}, and has been suggested as a candidate gene for the following phenotypes: autism\textsuperscript{21}, autosomal recessive severe intellectual disability, epilepsy, and dysarthria\textsuperscript{22}. More studies are needed to clarify the functions of \textit{UBR4} in the brain and its role in human neurological diseases. While the ubiquitin ligase N-recognins are reported to be important for cardiac development\textsuperscript{23}, \textit{UBR4} has so far not been shown to have a similar role. \textit{UBR4} is highly intolerant to loss of function variants with a pLI of 1.00 (GnomAD accession date October 18th, 2019). \textit{UBR4} is a strong candidate gene for the cognitive and behavioral symptoms in the proximal 1p36 deletion described here and might also be linked to ptosis and heart defects.

The \textit{CAPZB} gene (OMIM 601572) encodes the beta subunit of the CAPZ protein, an actin-capping protein involved in modulating actin filaments and cytoskeleton in sarcomeres in muscle. It has been shown to be important in embryogenesis, and regulates tissue morphogenesis and cell behavior.\textsuperscript{24} Clinical consequences of changes in this gene is largely unknown, however, a female infant with congenital cleft palate, micrognathia, muscular hypotonia, and developmental delay had a de novo reciprocal translocation t(1;13)(p36.13;q12.1) with the breakpoint on chromosome 1 located in the \textit{CAPZB}-gene.\textsuperscript{24} Studies on \textit{capzb}\textsuperscript{-/-} zebrafish support the involvement of the \textit{capzb}-gene in clefting and micrognathia. Malformations of craniofacial skeletal muscles were seen in \textit{capzb}\textsuperscript{-/-} zebrafish, while adult heterozygotes had subtle or no changes\textsuperscript{24}. While CAPZ plays a role in cardiac myofilament activation\textsuperscript{23}, no association to congenital heart malformation seems to exists with the current knowledge. \textit{CAPZB} can be predicted to be LoF sensitive as the pLI is 0.91 (GnomAD accession date October 18th, 2019). \textit{CAPZB} is also a candidate gene for at least some of the features of the 1p36 deletion.

In conclusion we present a new microdeletion syndrome at proximal 1p36 (1p36.13-1p36.12) characterized by learning disability or mild intellectual disability, speech delay, behavioral anomalies, and congenital ptosis. The smallest region of overlap is extended 1 Mb spanning from 19077793 bp to 20081292 bp (GRCh37; hg19). We consider the genes \textit{UBR4} and \textit{CAPZB} to be the best candidate genes for the common features. More studies are needed to describe the new deletion syndrome better and clarify the genotype-phenotype correlation.

References

Reference List


**Figure Legends**

**Figure 1:** Top: Photos of the reported individuals. Numbers refer to the numbers of the individuals in the study. Ages at the photos are: 1) 8 years, 2) 6 years, 3) 30 years, 4) 11 years, 5) 6 months, and 6) 16 years. The most consistent dysmorphic feature was ptosis or blepharophimosis as seen in individuals 1-5. Ptosis was mild in individual 2, while individuals 3, 4 and 5 had surgery for ptosis. Individuals 1-5 had pointed chin or “stuck-on chin”, while individual 6 had retrognathia. Bottom: 1p36 with the positions of the terminal deletion 1p36 and the proximal deletion 1p36 as described by Kang et al. indicated in hatched red. To the right deletions of the reported individuals of this paper and those with overlapping deletions identified from literature are shown in red, as is the smallest region of overlap (SRO). Please note that individual 8 only had a small overlap with the SRO (66 bp), this individual is not considered to have the 1p36 deletion syndrome defined here. Genes included in the SRO at chr1:19077793-20081292 (GRCh37/hg19) are shown with the two most likely candidate genes *UBR4* and *CAPZB* (not all isoforms) encircled.
<table>
<thead>
<tr>
<th>Table I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual 1</strong></td>
</tr>
<tr>
<td>Decipher ID</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Age at reporting</td>
</tr>
<tr>
<td>Deletion in bp (hg19)</td>
</tr>
<tr>
<td>Size of deletion</td>
</tr>
<tr>
<td>Inheritance</td>
</tr>
<tr>
<td>Cognition</td>
</tr>
<tr>
<td>Speech delay</td>
</tr>
<tr>
<td>Behavior</td>
</tr>
<tr>
<td>Motor problems</td>
</tr>
<tr>
<td>Age at walking</td>
</tr>
<tr>
<td>Congenital heart defects</td>
</tr>
<tr>
<td>Hearing and vision</td>
</tr>
<tr>
<td>Skeletal features</td>
</tr>
<tr>
<td>Other features</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Congenital ptosis</strong></td>
</tr>
<tr>
<td>Eye, other</td>
</tr>
<tr>
<td><strong>High palate</strong></td>
</tr>
<tr>
<td><strong>Teeth</strong></td>
</tr>
<tr>
<td><strong>Pointed chin</strong></td>
</tr>
<tr>
<td><strong>Hands and feet</strong></td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
</tbody>
</table>
### Table II

**Clinical features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Affected</th>
<th>Not Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual disability or learning disability</td>
<td>5/7</td>
<td>2/7</td>
</tr>
<tr>
<td>Speech delay</td>
<td>5/6</td>
<td>1/6</td>
</tr>
<tr>
<td>Motor delay</td>
<td>5/5</td>
<td>2/5</td>
</tr>
<tr>
<td>Behavioral anomalies</td>
<td>4/7</td>
<td>3/7</td>
</tr>
<tr>
<td>Congenital heart malformation</td>
<td>3/7</td>
<td>4/7</td>
</tr>
<tr>
<td>Congenital ptosis</td>
<td>5/7</td>
<td>2/7</td>
</tr>
<tr>
<td>Pointed or “stuck on” chin</td>
<td>6/7</td>
<td>1/7</td>
</tr>
<tr>
<td>High palate</td>
<td>4/5</td>
<td>3/5</td>
</tr>
<tr>
<td>Misalignment of teeth</td>
<td>3/4</td>
<td>4/4</td>
</tr>
</tbody>
</table>

Table I: Clinical features

Clinical information is given for individuals 1-7 with the new 1p36 microdeletion syndrome plus two cases from the literature with overlapping deletions. Please note that individual 8 only has a slight overlap with the SRO, she is not considered to have the new 1p36 microdeletion syndrome but might indicate that the SRO is slightly smaller than defined at present. MI= maternally inherited, ID = intellectual disability, LD = learning disability, - = no information, y = years, m = months, ASD = atrial septal defect, VSD = ventricular septal defect, BAV = bicuspid aortic valve, FOP = patent foramen ovale, DAP = persistent ductus arteriosus, pf = palpebral fissures. Kang, S.H., et al., 2007, Clin Genet. 72, 329-38; Zaveri, H.P., et al., 2014, PLoS One. 2014 Jan 15;9(1):e85600.

Table II: Overview of clinical features

Overview of features seen in three or more of the seven individuals with proximal 1p36 deletions with overlapping deletions and SRO chr1: 19077793-20081292 (hg19). Red = affected, grey = not affected.