European Journal of Medical Genetics xxx (2016) 1–6

Contents lists available at ScienceDirect

European Journal of Medical Genetics

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

Clinical features associated with *CTNNB1* de novo loss of function mutations in ten individuals

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ARTICLE INFO

Article history:
Received 15 August 2016
Received in revised form
18 November 2016
Accepted 28 November 2016
Available online xxx

Keywords:
CTNNB1
Intellectual disability
Microcephaly

ABSTRACT

Loss of function mutations in *CTNNB1* have been reported in individuals with intellectual disability [MIM #615075] associated with peripheral spasticity, microcephaly and central hypotonia, suggesting a recognisable phenotype associated with haploinsufficiency for this gene. Trio based whole exome sequencing via the Deciphering Developmental Disorders (DDD) study has identified eleven further individuals with de novo loss of function mutations in *CTNNB1*. Here we report detailed phenotypic information on ten of these. We confirm the features that have been previously described and further delineate the skin and hair findings, including fair skin and fair and sparse hair with unusual patterning.

1. Introduction

Whole exome sequencing is increasingly being utilised in the investigation of intellectual disability (ID), with more genes being implicated as a result. A gene, recently linked to a syndromic form of ID, is *CTNNB1*, which encodes for beta 1 catenin. This is a component of the cadherin adhesion complex which mediates cell-cell adhesion, and is also part of the Wnt signalling pathway. This pathway is important in controlling cell growth and differentiation, both in normal and tumour tissue. Beta catenin knockout mice display behaviours consistent with autistic spectrum disorder (Dong et al., 2016), as well as defects in neural development (Brault et al., 2001) and in hair follicle formation (Huelsken et al., 2001). Somatic mutations in *CTNNB1* have been detected in certain tumours, and more recently germline, loss of function mutations have been linked to intellectual disability [MIM #615075].

Mutations in *CTNNB1* were first linked to intellectual disability when it was identified as a candidate gene during a trio exome sequencing study of 100 patients with intellectual disability (de Ligt et al., 2012). One patient was found to have a frameshift mutation (p.Ser425Thr*fs**11), with a further two patients found to have nonsense mutations (p.Arg515* and p.Gln309*) on sequencing of an additional cohort of 765 patients with intellectual disability. The phenotypes of these three patients were investigated in detail, and features included mild to severe intellectual disability, craniofacial anomalies, severe speech delay, microcephaly and childhood hypotonia with progressive peripheral spasticity and delayed motor

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http://dx.doi.org/10.1016/j.ejmg.2016.11.008
1769-7212/

development (Tucci et al., 2014). A report providing details of a patient with a whole gene deletion of *CTNNB1*, along with a further case series of 16 individuals with loss of function mutations in *CTNNB1*, confirmed these phenotypic features, as well as providing more detail regarding associated dysmorphic features, including thin upper lip vermillion and small alae nasi (Dubruc et al., 2014; Kuechler et al., 2015). One further case of a patient with a de novo nonsense mutation in *CTNNB1* has been reported, presenting with characteristic features such as microcephaly, peripheral spasticity and delayed speech, along with atypical features of hyperekplexia and apraxia of upward gaze (Winczewska-Wiktor et al., 2016). This case series aims to further delineate the phenotype associated with loss of function mutations in *CTNNB1*, reviewing ten patients ascertained through the Deciphering Developmental Disorders study.

2. Methods

The Deciphering Developmental Disorders (DDD) study is a project which recruited patients through genetics centres in the UK and Ireland, with the aim to utilise genome-wide microarray and whole exome sequencing to increase diagnostic rates for children and adults with severe undiagnosed developmental disorders. Specifically congenital or early onset severe phenotypes were the focus for recruitment, with family trios sampled in the majority of cases. 13,632 families were recruited, and analysis of 4293 has been completed so far. DNA samples from patients and their parents were analysed at the Wellcome Trust Sanger Institute with microarray analysis (Agilent 2 × 1M array CGH [Santa Clara, CA, USA] and Illumina 800K SNP genotyping [San Diego, CA, USA]) to identify copy number variants (CNVs) in the child, and exome sequencing (Agilent SureSelect 55 MB Exome Plus with Illumina HiSeq) to investigate single nucleotide variants (SNVs), small insertion-deletions (indels), and CNVs in coding regions of the genome. An automated variant filtering pipeline was used to narrow down the number of putative diagnostic variants, by ruling out common and non-functional variants, and then comparing variants against an in-house database of genes consistently implicated in specific developmental disorders, the Developmental Disorders Genotype-to-Phenotype database (DDG2P). This database includes more than 1000 genes that have been consistently implicated in specific developmental disorders and is updated regularly with newly implicated genes (Wright et al., 2015).

By interrogating the DECIPHER database, where DDD results can be scrutinised, we identified eleven patients with an inactivating mutation of *CTNNB1*. We then contacted the responsible clinicians to obtain detailed phenotypic data on these patients, and received responses for ten patients. Consent was obtained for publication of photographs.

2.1. Clinical features

The patients' ages range from 3 to 27 years, with three males and seven females. In all patients symptoms occurred within the first year of life. Table 1 shows the pertinent clinical features for each patient.

2.2. Craniofacial

Mild dysmorphic features have been previously reported. Our patients displayed a range of features, with a thin upper lip being the most common (7/10 patients). Other features seen include low set ears, wide spaced teeth, prominent columella (previously noted in older patients) and a prominent nose (Fig. 1). Dubruc et al.'s case report noted that a patient with a whole gene deletion of *CTNNB1* had fair, sparse hair and fair skin, and so we specifically asked about these features when collecting clinical details. 6/10 patients were reported to have fair skin, and 7/10 patients were reported to have fair and/or fine hair compared to other family members, with two of those having an unusual hair pattern such as a cowlick or unusual hair whorl.

2.3. Growth

3/10 patients were noted to have intrauterine growth retardation on antenatal scanning. Postnatal microcephaly was a common finding, with 7/10 patients having a head circumference of −3 standard deviations or smaller. Fig. 2 visualises the growth parameters and developmental progress of the 11 patients ascertained through the DDD study.

2.4. Development

All of the patients have significant motor delay, with the earliest age of walking at 2.5 years. 3/10 patients are unable to walk independently, the oldest being 6 years 2 months of age. All of the patients have significant speech delay, as has previously been reported. Behavioural problems are a common feature, with 9/10 patients reported to have issues such as aggressive outbursts and poor sleep. Visual problems have previously been reported, and 4/10 patients have strabismus, with 2/10 also affected by hypermetropia.

2.5. Neurology

As noted in previous reports, 9/10 patients were noted to have truncal hypotonia, usually presenting within the first year of life. 2/10 patients had problems feeding in the neonatal period. Peripheral spasticity is a common feature which seems to present after initial hypotonia, with 7/10 patients developing this feature. 2/10 patients were noted to have broad based or ataxic gait, which became evident at 3–4 years of age. Dystonic posturing was also noted in 2/10 patients, presenting at 18 months to 2 years of age. None of our patients were reported to have seizures; there was a query regarding possible absence seizures in 1 patient, but EEG was normal. All 10 patients have had MRI brain scans, which were normal except for 1 patient, who was noted to have atrophy of the left temporal lobe.

2.6. Mutations

In our patients, 8 nonsense and 2 frameshift de novo mutations were detected in the *CTNNB1* gene by whole exome sequencing of family trios (Table 1). These are all predicted to lead to premature truncation of the protein. This concurs with previously reported mutations and deletions, which were all de novo and caused loss of function of the gene.

3. Discussion

Our case series reinforces the phenotypic features previously reported in conjunction with inactivating *CTNNB1* mutations, including intellectual disability, postnatal microcephaly, truncal hypotonia and peripheral spasticity, mild dysmorphic features and behavioural problems. An additional patient with a *CTNNB1* loss of function mutation identified by the DDD study also displays typical phenotypic features when looking at the DECIPHER database; we have not included this patient in our clinical report as we were not able to collect further updated phenotypic data for them. This patient (DECIPHER ID 264,159), who has a de novo frameshift variant

Please cite this article in press as: Kharbanda, M., et al., Clinical features associated with *CTNNB1* de novo loss of function mutations in ten individuals, European Journal of Medical Genetics (2016), http://dx.doi.org/10.1016/j.ejmg.2016.11.008