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Clinical research

Clinical characterization, genetic mapping and whole-genome sequence analysis of a novel autosomal recessive intellectual disability syndrome

Eevi Kaasinen [a,1], Elisa Rahikkala [b,1], Peppi Koivunen [c], Sirpa Miettinen [b], Mirjam M.C. Wamelink [d], Mervi Aavikko [a], Kimmo Palin [a], Johanna Myllyharju [c], Jukka S. Moilanen [b], Leila Pajunen [b], Auli Karhu [a], Lauri A. Aaltonen [a,*]

[a] Department of Medical Genetics, Genome-Scale Biology Research Program, University of Helsinki and Haartman Institute, Helsinki, Finland
[b] Department of Clinical Genetics, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland
[c] Biocenter Oulu, Oulu Center for Cell-Matrix Research, Faculty of Biochemistry and Molecular Medicine, University of Oulu, Finland
[d] Department of Clinical Chemistry, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

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ABSTRACT

We identified six patients presenting with a strikingly similar clinical phenotype of profound syndromic intellectual disability of unknown etiology. All patients lived in the same village. Extensive genealogical work revealed that the healthy parents of the patients were all distantly related to a common ancestor from the 17th century, suggesting autosomal recessive inheritance. In addition to intellectual disability, the clinical features included hypotonia, strabismus, difficulty to fix the eyes to an object, planovalgus in the feet, mild contractures in elbow joints, interphalangeal joint hypermobility and coarse facial features that develop gradually during childhood. The clinical phenotype did not fit any known syndrome. Genome-wide SNP genotyping of the patients and genetic mapping revealed the longest shared homozygosity at 3p22.1-3p21.1 encompassing 11.5 Mb, with no other credible candidate loci emerging. Single point parametric linkage analysis showed logarithm of the odds score of 11 for the homozygous region, thus identifying a novel intellectual disability predisposition locus. Whole-genome sequencing of one affected individual pinpointed three genes with potentially protein damaging homozygous sequence changes within the predisposition locus: *transketolase* (*TKT*), *prolyl 4-hydroxylase transmembrane* (*P4HTM*), and *ubiquitin specific peptidase 4* (*USP4*). The changes were found in heterozygous form with 0.3–0.7% allele frequencies in 402 whole-genome sequenced controls from the north-east of Finland. No homozygotes were found in this nor additional control data sets. Our study facilitates clinical and molecular diagnosis of patients with this novel autosomal recessive intellectual disability syndrome. However, further studies are needed to unambiguously identify the underlying genetic defect.

1. Introduction

Intellectual disability (ID, also known as mental retardation) is considered as early onset cognitive impairment caused by environmental or genetic factors, yet precise etiology is known for ~40% of cases [Rauch et al., 2006]. Most severe forms of ID [intelligence quotient (IQ) less than 50] often have chromosomal or single-gene causes. X-chromosomal recessive gene defects are estimated to account for ~10% of ID [Ropers, 2010]. Recently, high-throughput sequencing has revealed numerous novel genes for either autosomal dominant *de novo* ID or autosomal recessive ID [de Ligt et al., 2012; Musante and Ropers, 2014; Najmabadi et al., 2011], demonstrating that the etiology of ID is genetically extremely heterogenous.

Homozygosity mapping in consanguineous families is a powerful method for localizing genetic defects for autosomal recessive diseases. However, many patients with recessive diseases emerge as isolated cases due to small family sizes in Western societies hampering genetic studies. The late-settlement population from the north-east of Finland is a well-characterized isolate which

* Corresponding author. Department of Medical Genetics, Biomedicum Helsinki, Haartmaninkatu 8, P.O. Box 63, 00014 University of Helsinki, Finland. Tel.: +358 2941 25595; fax: +358 2941 25610.
E-mail address: lauri.aaltonen@helsinki.fi (L.A. Aaltonen).
[1] These authors are joint first authors.

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exhibits high linkage disequilibrium as compared with other isolates worldwide, and mean genome homozygosity of 2.0% as compared to 0.9% in the early-settlement population of Finland [Jakkula et al., 2008]. These characteristics are explained by low number of founders in the population history, and enable detection of rare mutations in homozygous form in patients with autosomal recessive diseases.

In Northern Finland, prevalence estimate of severe ID was 6.3 per 1000 persons in a one-year birth cohort [Rantakallio and von Wendt, 1986]. In this study we report a previously uncharacterized profound ID syndrome in an extended pedigree from the north-east of Finland. Six patients were identified with a highly similar syndromic ID phenotype, and their parents were all distantly related to a common ancestor from the 17th century, suggesting autosomal recessive inheritance. The aim of this work was to characterize the clinical features of the condition, as well as to map and to identify the predisposition locus.

2. Patient data

Six patients (Patients 1–6) had developed an unexplained syndromic form of profound ID (Table 1). Patients were born healthy from uneventful pregnancies at normal gestational weeks (Supplementary Table 1) to healthy parents. Etiological investigations including chromosome and array-CGH analysis, and metabolic screening (urine amino acids, organic acids and oligosaccharides, and plasma amino acids) showed normal results, which led us to suspect a novel syndrome. Fragile-X DNA analysis and Prader-Willi methylation analysis also showed normal results. Brain MRI of Patients 1, 3 and 4 showed normal brain structures; Patient 2 had Chiari I malformation. No other congenital malformations were noted. The patients lived in the same village in the north-east of Finland, and subsequent genealogical work showed that they all belong to a large consanguineous family (Fig. 1). One patient (Patient 6) had three deceased siblings with ID, but no patient records were available and no autopsies were performed. Furthermore, one deceased individual (Patient 7) with profound ID was identified in the extended pedigree.

Patient 1 (XII-4 in Figs. 1 and 2a, b and c) is a 27-year-old male. He learned to walk without support at the age of 3.5 years. He understands and can express himself by simple sentences and gestures. At the age of 16 years his developmental age was assessed to correspond to 1 year and 6 months (Cattell Infant Intelligence Scale, CIIS) [Atkinson, 1990].

In ophthalmological examination at the age of 5 months rotatory pendular nystagmus and exotropy of the left eye was noted. At the age of 1 year and 2 months strabismus surgery of his left eye was undertaken including retropositioning of the lateral rectus muscle and resection of the medial rectus muscle. At the age of 9 years he had alternating exotropia. He had eyeglasses for myopia and astigmatism. Retinal pigment color was reported to be lighter than normal. Visual evoked potentials (VEPs) were normal. Electroretinogram (ERG) showed low responses, suggestive of abnormal retinal function.

At the age of 23 years he started to have weekly attacks of aggressive behavior during the nights while sleeping. A REM sleep behavior disorder was clinically suspected and a small dose of diazepam in the evening stopped the nocturnal aggressive behavior. Electroencephalography (EEG) showed a moderate background abnormality, but no epileptiform changes.

Patient 2 (XII-5 in Figs. 1 and 2d and e) is a 25-year-old female. She never learned to talk or walk unsupported. She uses a wheelchair and moves on her own by crawling or walking supported by another person. She expresses herself using gestures, laughter and vocalizing. In the psychological assessment at the age of 15 years using the revised Bayley Scales of Infant Development (BSID-II) her developmental age was assessed to correspond to 9–10 months.

After birth she had seizures associated with an opistotonus position and phenobarbital medication was initiated. At the age of 10 years an EEG showed focal epileptiform discharges in the occipitotemporoparietal area and carbamazepine medication was initiated. Carbamazepine caused sleepiness and it was replaced by lamotrigine medication.

She has a poor eye contact and alternating exotropia in both eyes. Retinal pigment was reported to be lighter colored than normal. An ERG at the age of 6 months showed abnormal

Table 1
Common clinical characteristics of the patients.

Patient	Patient 1 (XII-4)	Patient 2 (XII-5)	Patient 3 (XII-6)	Patient 4 (XII-1)	Patient 5 (XI-3)	Patient 6 (XI-7)
Sibship	Sibship 1	Sibship 1	Sibship 1	Sibship 2	Sibship 3	Sibship 4
First presentation (symptom and age)	Strabismus since birth, generalized muscle hypotonia noted at infancy	Marked hypotonia noted already after birth	Hypotonia and strabismus since birth	Hypotonia and strabismus since infancy	At the age of 6 months mother noted that her development was not normal	nd
Severity of intellectual disability	Profound	Profound	Profound	Profound	Profound	Profound
Hypotonia	+	+	+	+	+	+
Coarse facial features	+	+	+	+	+	+
Strabismus	+	+	+	+	+	+
Finger joint hypermobility	+	+	+	+	+	+
Planovalgus of the ankles	+	+	+	+	+	+
Valgus of the knees	+	+	+	+	+	+
Contracture in the elbow joints	+	+	+	+	+	+
Flexion in the hips and knees when walking	+	nd (cannot walk)	+	+	+	nd (cannot walk)
Tendency to obesity[a]	+	+	+	+	+	−
Epilepsy	−	+	+	−	+	+
Sleep behaviour disorder	+	−	−	+	−	−

nd: not determined.
[a] Significant obesity currently (as presented in Supplementary Table 1) or during childhood.