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Short clinical report

Acrocallosal syndrome: Identification of a novel *KIF7* mutation and evidence for oligogenic inheritance

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ABSTRACT

Objective: Acrocallosal syndrome (ACLS) is a rare genetically heterogeneous disorder characterised by a variety of developmental anomalies including agenesis or hypoplasia of the corpus callosum. ACLS and the related disorder, hydrolethalus syndrome, have recently been reported to be caused by mutations in the *KIF7* gene. In the present study we report a 15 year follow up of a consanguineous family with ACLS and the results of exome sequencing.
Results: A novel in-frame deletion *KIF7* mutation (p.218-221del) was detected. This is the first deletion mutation in *KIF7* described in ACLS and is predicted to disrupt the KIF7 protein within the kinesin motor domain. Also present, in addition to the homozygous *KIF7* mutation, were loss of function variants in known ciliopathy genes; *AHI1* (p.R830W), *BBS2* (p.N70S) and *BBS4* (p.M472V).
Conclusion: KIF7 has previously been demonstrated to regulate function of primary cilia and ACLS is now categorised as a ciliopathy – a group of disorders in which oligogenic disease is frequent. The finding of known loss of function variants in ciliopathy associated genes, *AHI1*, *BBS2* and *BBS4* in addition to *KIF7* mutations provides evidence for oligogenic inheritance in ACLS and suggests that this might contribute to the phenotypic variability of *KIF7*-related disorders.

1. Introduction

Acrocallosal syndrome (ACLS) was first described in 1979 [1]; it is now recognized as a rare and genetically heterogeneous autosomal recessively inherited disorder that is characterised by craniofacial dysmorphism, agenesis or hypoplasia of the corpus callosum and duplication of the phalanges of the hallux/or thumbs [2]. In addition, polysyndactyly and learning disabilities are common [3]. The clinical features of ACLS overlap with those of Greig cephalopolysyndactyly syndrome and Hydrolethalus syndrome (HLS) [4,5]. Recently, homozygous mutations in the *KIF7* gene were described in patients with HLS and ACLS [5]. We now describe a 15 year follow up of a family with ACLS and confirm that *KIF7* mutations can cause ACLS.

2. Subjects and methods

2.1. Clinical report

At the time of the original report the consanguineous family of Israeli–Arab extraction comprised three siblings (one deceased) with ACLS, 5 unaffected siblings and a further deceased sibling with possible ACLS. The affected sibling investigated in this report was listed as patient 2 in the previous report and at that time the clinical history was of a male child, born after an uneventful pregnancy and delivery.

At birth the child presented with macrocephaly, a wide anterior fontanelle, hypertelorism, polydactyly of hands and feet, hypogenitalism, cryptorchidism and congenital dislocation of the hips. At age 6 years he was severely retarded, without speech, markedly hypotonic and unable to stand or walk. His head circumference, and inner- and outer canthal distances were above the 97th percentile. Dysmorphic signs included downslanting palpebral fissures; short philtrum with upturned upper lip; open mouth with normal palate; normally shaped

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and posteriorly rotated ears and a broad and prominent forehead. There was hypogenitalism with bilateral cryptorchidism. Both hands showed only slight syndactyly between fingers three and four and clinodactyly of both fifth fingers. Pre-axial polysyndactyly was present in the right foot. Computed brain tomography showed absence of the corpus callosum, enlarged ventricles and cortical atrophy.

At age 9 years a seizure disorder was diagnosed. Physical examination demonstrated head circumference, inter- and outer canthal distances were on the 97th percentile; height and weight between the 25th and 50th percentiles. Abnormal signs detected included macrocephaly with frontal bossing, hypertelorism, short nose, broad nasal bridge and anteverted nostrils; short philtrum with upturned upper lip; open mouth, a high and narrow palate; posteriorly rotated ears with fully developed segments and bilateral lobe creases; a small penis with hypoplastic scrotum; complete postaxial polydactyly of the right hand and rudimentary polydactyly of the left hand; bilateral duplicated first toes and postaxial polydactyly of the left foot. Radiographs demonstrated duplication of the proximal and distal phalanges and first metatarsal bones and an extra rudimentary bone between the first and second metatarsals. Computed brain tomography showed agenesis of corpus callosum and enlarged ventricles without signs of hydrocephaly.

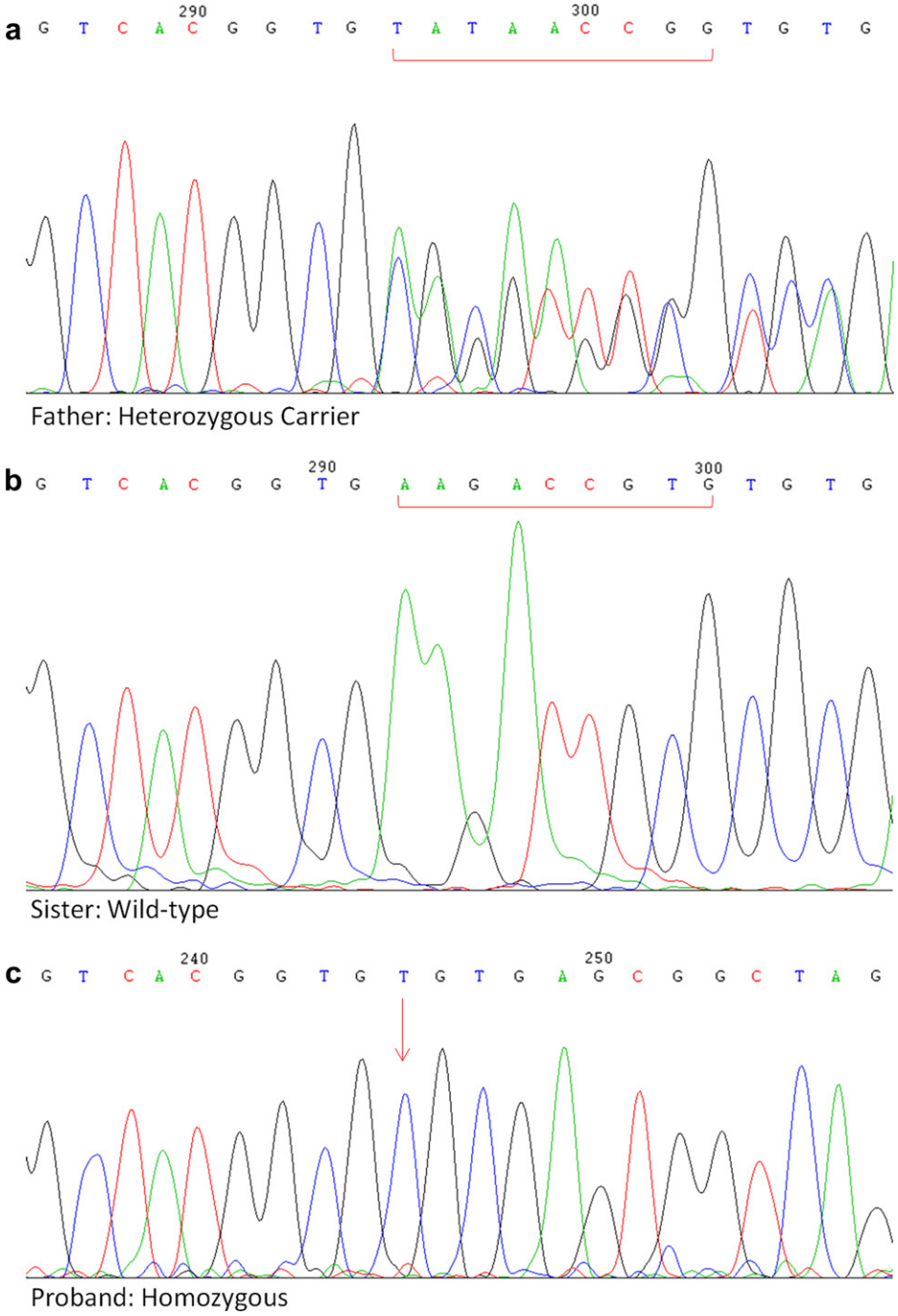

Fig. 1. Electropherograms of several members from the family. (a) The electropherograms of the father clearly show that he is a heterozygous carrier for the mutation, marked by the red bracket. (b) The sister of the proband shows the wildtype genotype, marked by the red bracket. (c) Finally, if the electropherogram of the proband is compared to the other family members, it can clearly be seen that there is a deletion of 9 nucleotides, marked by the red arrow.