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SHORT COMMUNICATION

A novel *ISLR2*-linked autosomal recessive syndrome of congenital hydrocephalus, arthrogryposis and abdominal distension

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Abstract

ISLR2 (immunoglobulin superfamily containing leucine-rich repeat 2), encodes a protein involved in axon guidance in brain development (hence the other name leucine-rich repeat domain- and immunoglobulin domain-containing axon extension proteins; LINX). A recently described mouse knockout displays hydrocephalus. However, the corresponding phenotype in humans is unknown. Here, we describe a multiplex consanguineous family in which a homozygous truncating variant in *ISLR2* segregates with severe congenital hydrocephalus, arthrogryposis multiplex congenita and abdominal distension. We suggest this syndrome may represent the human "knockout" phenotype for *ISLR2*.

Short communication

Congenital hydrocephalus is an important birth defect of brain development. While many Mendelian syndromic forms of congenital hydrocephalus have been described, the combination of congenital hydrocephalus and arthrogryposis has only rarely been reported, e.g. Alkuraya–Kucinskas syndrome (MIM: 617822), Fowler syndrome (MIM: 225790), Walker–Warburg syndrome (MIM: 236670), Marden–Walker syndrome (MIM: 248700), and Aase and Smith syndrome (MIM: 147800). Here, we describe a multiplex consanguineous family in which an apparently novel syndrome of congenital hydrocephalus, arthrogryposis and abdominal distension seems to represent the human *ISLR2* "knockout" phenotype.

The proband (IV:6), the product of parents' 6th pregnancy, was delivered by elective caesarian section (C/S) indicated by previous C/S and hydrocephalus detected by antenatal ultrasound scan. Parents are Saudi first cousins who had lost two children (IV:1 and IV:5), in addition to another (IV:7) who was born later. They have two healthy children (IV:2 and IV:3), followed by one abortion (IV:4) (Fig. 1a). All the four affected children presented with the same phenotypic features, namely hydrocephalus, arthrogryposis multiplex congenital (AMC), and non-obstructive abdominal distension, which was shown in one of them (IV:5) by rectal biopsy to be due to aganglionosis (Fig. 1i–j). The proband displayed severe hydrocephalus [occipitofrontal circumference 41.5 cm (+3.2 SD)], frontal bossing, widely separated sutures, and wide fontanelles, low set ears (Fig. 1b), arthrogryposis of both upper and lower limbs with fixed extension of the arms, clenched hands with adducted thumbs (cortical thumbs) (Fig. 1d) and fixed flexion of legs and talipes equinovarus deformities (TEV) of both feet (Fig. 1c). Neurologic examination revealed generalized hypotonia with diminished reflexes. Ophthalmologic examination showed cupping of the fundi. Other systems were normal. When started on full enteral feeding, she developed severe abdominal distention. Hirschsprung disease was suspected because her brother (IV:5) had a similar presentation and was found to have Hirschsprung disease on rectal biopsy (Fig. 1i–j). Rectal biopsy on the proband, however, showed no evidence of aganglionosis. No other causes of abdominal distension were identified. Ventriculoperitoneal shunt was inserted. She developed convulsions controlled

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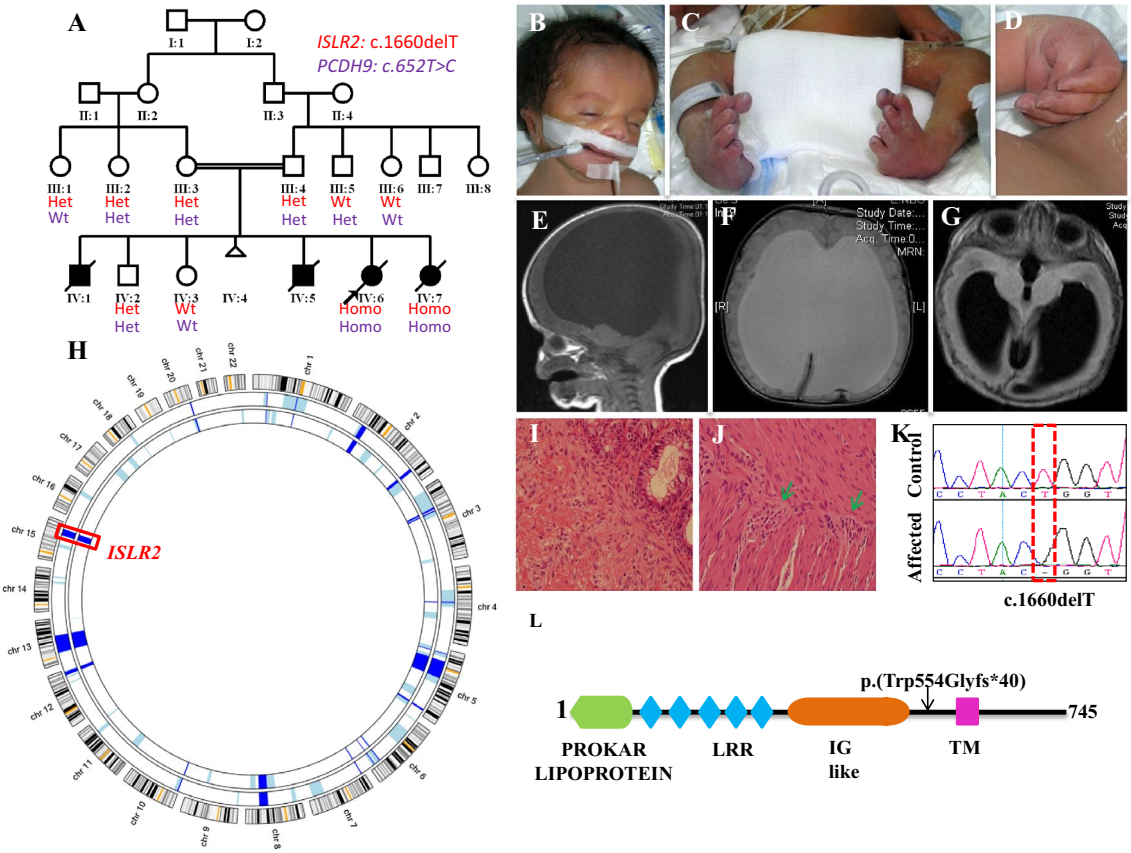

Fig. 1 **a** Pedigree of the family and their genotypes for both variants in *ISLR2* and *PCDH9*. **b–d** Clinical images of the index (IV:6) showing macrocephaly, depressed nasal bridge, bilateral TEV and arthrogryposis of hands. **e–g** MRI images showing hydrocephalus. **h** Circular ideogram of the available affected members' genome (Agile MultiIdeogram; http://dna.leeds.ac.uk/) showing all shared homozygous regions in blue color (*ISLR2* locus is highlighted with red box). **i–j** Rectal biopsy (from IV:5) (H&E staining, 20× magnification) from the patient showing the contrast between the aganglionic (**i**) and ganglionic (**j**, green arrows mark ganglion cells) segments. **k** Sequence chromatogram showing deletion of T. **l** ISLR2 protein structure showing the mutation and functional domains: prokaryotic lipoprotein domain (1–20) regulates signal transduction and protein folding, LRR (leucine-rich repeat; 52–193) regulates protein folding, Ig-like domain (233–371) regulates cell–cell recognition, transmembrane region (591–613) allows the transport of substances across the cell membrane. *Homo* homozygous, *Het* heterozygous, *Wt* wild type

by phenobarbitone. Creatine kinase was normal, and muscle biopsy (left vastus lateralis) showed non-specific myopathy. MRI of the brain (Fig. 1e–g) revealed severe supratentorial hydrocephalus with grossly dilated lateral and 3rd ventricles, and normal 4th ventricle and cisterna magna, suggestive of obstruction due to aqueduct stenosis. Chromosome analysis revealed normal female karyotype 46,XX. Metabolic screen was negative. She died at the age of 2 months with sepsis and toxic megacolon. The first child (IV:1) also developed severe abdominal distension and toxic megacolon (no rectal biopsy was performed), in addition to hydrocephalus and arthrogryposis and died at the age of 4 months. To summarize, all the four affected children presented with the same triad of hydrocephalus, arthrogryposis multiplex congenital (AMC), abdominal distension, and death in early infancy.

Informed consent was obtained (King Faisal Specialist Hospital and Research Centre, RAC# 2080 006). Blood samples were available from the two affected (IV:6 and IV:7) and two unaffected children (IV:2; IV:3), the parents, and four paternal and maternal unaffected relatives. Autozygome analysis of all available family members, exome sequencing of the proband and autozygome-guided filtering of variants were as described before (Alkuraya 2013). Only two novel (absent in gnomAD and a local database of ~2300 exomes) homozygous variants within the candidate autozygome fully segregated with the disease in the family: a missense (*PCDH9*: NM_020403.4:c.652T > C:p.(Tyr218His)) and a frameshift deletion (*ISLR2* NM_020851.2:c.1660delT:p.(Trp554Glyfs*40)). The phenotype of *Pcdh9*$^{-/-}$ is limited to specific deficits in long-term social and object recognition, which makes the *PCDH9* variant an unlikely candidate, although we cannot exclude its contribution in view of its involvement in brain development (Bruining et al. 2015). On the other hand, we suggest that the phenotype

of *Islr2*$^{-/-}$ (severe congenital hydrocephalus (Abudureyimu et al. 2018)) and the truncating nature of the mutation argue strongly in favor of *ISLR2* as the gene underlying this syndrome. Of note, no pathogenic variants were identified in *RET*, a major gene in Hirschsprung disease pathogenesis (see below).

ISLR2 (also known as *LINX*) is only expressed in neurons and testes (Abudureyimu et al. 2018). While the first knockout mouse had impaired development of the internal capsule and no hydrocephalus (Mandai et al. 2014), a much more recent independent knockout mouse was shown to additionally have severe hydrocephalus (Abudureyimu et al. 2018). Although the mechanism remains unclear, it may be related to the role of ISLR2 in reorganizing the cytoskeleton of developing neurons (Abudureyimu et al. 2018). The relationship between ISLR2 and Hirschsprung disease is less clear since intestinal aganglionosis was only documented in one of the four affected children, although we note that ISLR2 has been shown to bind RET (Abudureyimu et al. 2018; Mandai et al. 2009), which accounts for nearly 50% of the heritable risk for Hirschsprung disease. Arthrogryposis is not described in *Islr2*$^{-/-}$ mouse models, nor are abnormalities of the gastrointestinal system so it remains to be seen if the progressive abdominal distension observed in the study family is recapitulated by these models. Future families with different biallelic variants in *ISLR2* will be required to confirm the proposed link to the syndrome we describe here, and to delineate its full phenotypic spectrum.

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

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