Journal of Human Genetics (2017) 62, 1005–1006

www.nature.com/jhg

CORRESPONDENCE

A novel *de novo* mutation in *CSNK2A1*: reinforcing the link to neurodevelopmental abnormalities and dysmorphic features

Journal of Human Genetics (2017) **62,** 1005–1006; doi:10.1038/jhg.2017.73; published online 20 July 2017

Approximately 2–5% of children are born with congenital abnormalities that manifest into more severe neurodevelopmental problems as they age.[1] Neurodevelopmental disorders encompass a wide range of severity and behavioral differences, many of which arise from *de novo* mutations in critical genes during early brain development.[2,3] Exome sequencing has been an effective means of diagnosing patients with similar neurodevelopmental disorders. The molecular diagnosis can be a way to shift from a more phenotype-driven management of the symptoms to a more refined treatment based on genotype.[4]

CASE REPORT

We report a 7-year-old German boy with a novel, *de novo CSNK2A1* germline mutation. He was born as the first child of a healthy 27-year-old mother and a healthy 31-year-old father (Figure 1a). After normal pregnancy, he was delivered preterm (35 weeks +3 days of gestation) and birth measurements were: weight 3220 g (+1.4 s.d.), length 50.0 cm (+0.8 s.d.) and OFC 32.0 cm (−0.7 s.d.). The patient needed feeding by nasogastric tube for 14 days after delivery. The pediatricians suspected Down syndrome in the newborn period. Microcephaly became evident in the first 1–2 years of life (−2.8 s.d.). The motor development (first steps at age 22 months) and speech development (around 100 words at age 3 years) were both delayed. At last examination at age 6 years and 7 months, the patient presented with global developmental delay, intellectual impairment, borderline microcephaly (OFC 49 cm, −1.9 s.d.), brachycephaly and dysmorphic features (Figure 1b). The patient was tested according to the German version of the social responsiveness scale (SRS) by John N Constantino. This test method is a questionnaire for children between ages 4 and 18 years and is used to measure autistic traits. His *T*-Value is 74, meaning he has a mild to moderately severe impairment of social responsiveness. The BUEVA test shows underperformance in the sections: general intelligence, sensorimotor function, expressive speech and regard. Furthermore, it shows average performance in the two sections articulation and receptive language. In addition, sleeping difficulties and hyperactive behavior were reported. EEG was unremarkable, cerebral MRI showed a 'solid lesion of the pineal gland with minor cystic inclusions', which was not considered clinically significant (Supplementary Figure 1).

GENETIC ANALYSIS

Exome sequencing was performed for the patient and his unaffected parents (trio), for which the parents gave written informed consent. Prior to exome sequencing, conventional cytogenetic and molecular analyzes were performed and showed normal results (Supplementary Table 1). After applying standard filtering criteria (*de novo* exonic or splicing mutation, frequency in ExAC or 1000 genomes <0.01, quality index >50, <4 times found in 'in-house' exomes and high CADD score >15) (Supplementary Figure 2), we identified four gene candidates, *RHOU*, *STAT2*, *CSNK2A1* and *PDGFRL*. However, only two mutations were confirmed to be real and *de novo*: STAT2 p.R807G, CSNK2A1 p.D156H (Supplementary Table 2). STAT2 is involved in mitochondrial neurological deterioration, but with a lower CADD score compared to CSNK2A1 and CSNK2A1 have recently been linked to a rare neurodevelopmental disorder and was predicted to be the most damaging change, CADD score 28.6 (Supplementary Table 2).[2,5]Specifically, 13 patients with neurodevelopmental disorders and *de novo CSNK2A1* mutations have been reported and variations within this gene are associated with developmental disorders at the genome-wide level.[2,5] The *de novo* mutation in our patient was confirmed by Sanger sequencing. CSNK2A1 p.D156H is located in the active site of protein and the aspartate residue at position 156 is also highly conserved. (GERP score 5.12; Figure 1c and d).

DISCUSSION

CSNK2A1 encodes the alpha (α) subunit of protein kinase CK2 (also known as Casein kinase 2).[6] Protein kinase CK2 is a ubiquitous serine/threonine, tetrameric kinase that is made of two regulatory beta and two catalytic alpha subunits. The α-subunit is highly expressed in the brain even in early embryonic stages.[7] All previously reported mutations reside in the glycine-rich ATP/GTP binding loop or the activation segment which influence regulation and activation of CK2α, having an important role stretching and collapsing the protein conformation according to the activation state of CK2α site (Figure 1c).[8] The mutation we identified is novel and resides in the active site of CSNK2A1 that may directly influence activation of the protein or even the higher-order tetramer structure of protein kinase CK2. Notably, the patients phenotype in this study overlaps with the five patients from the original study with delayed psychomotor development, behavioral problems, intellectual disability and dysmorphic features (Supplementary Figure 3).[5]

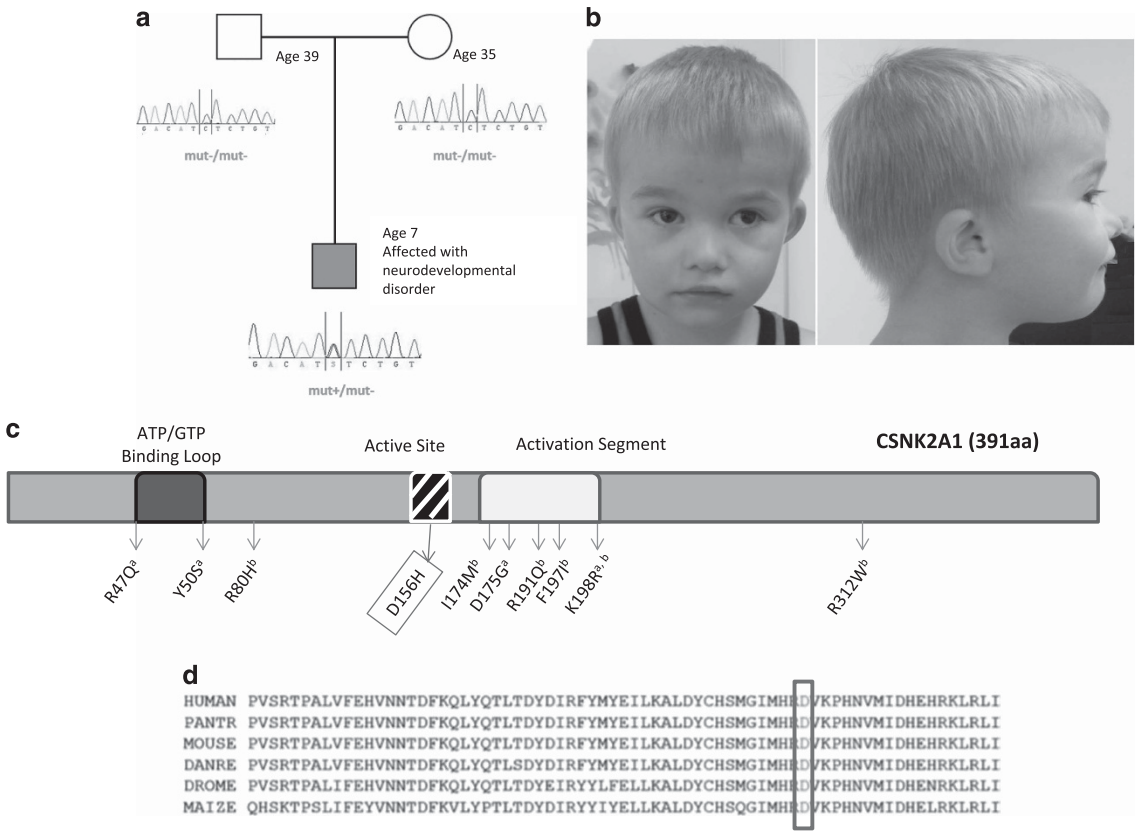

Figure 1 *De novo* CSNK2A1 p.D165H mutation. (**a**) Pedigree of trio and electropherogram of Sanger sequencing. Index patient is affected (filled-in). CSNK2A1 p.D165H mutation is represented as mut+, no mutation represented by mut–. (**b**) Photographs of the patient at the age of 4 years indicating strabism, as well as the patients craniofacial features: deep set eyes, depressed nasal bridge, prominent forehead, brachycephaly, small fleshy posteriorly rotated ears. (**c**) Domains of CSNK2A1 and locations of reported *de novo* variants. CSNK2A1 p.D156H identified in this study is shown in the active site (white stripes). Other identified mutations are situated in ATP/GTP binding loop (black), activation segment (white), and two mutations are not situated at a domain (blue). Superscript a: mutations identified in original paper,[5] superscript b: mutations identified in large consortium paper[2]. (**d**) Sequence alignment of the active site shows high conservation (outlined in red, letters in green). A full color version of this figure is available at the *Journal of Human Genetics* journal online.

Thus, our data support the pathogenicity of variants in *CSNK2A1*, especially within domains that influence protein activation states.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This research was supported by the Foundation of the University Medical Center Schleswig Holstein 'Gutes Tun!' (IH).

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Supplementary Information accompanies the paper on Journal of Human Genetics website (http://www.nature.com/jhg)