Rare & Inherited Disease Genomic Laboratory
Great Ormond Street Hospital for Children NHS Foundation Trust
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Director: 0Minder001 Doncas002 FRCPath
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GOSH - Neurology Great Ormond St Hospital NHS Foundation Trust Great Ormond Street London England WC1N 6HH	Patient Name: Mickey321, Mouse123 Patient DOB: 20/8/2014 Patient Gender: Male NHS Number: M356 128 7497 GOSH MRN: A3068479 Family Number: 00714053 External Pat ID: 0000714053

REFERRAL REASON:

Early onset or syndromic epilepsy

Variant sequence screening in Mickey321, Mouse123 due to severe difficulties in learning of onset in non-verbal mild pyramidal signs of obesity, epilepsy of atypical presences and an autism of learning challenges of the paternal side.

Result Summary

Consistent with a diagnosis of autosomal DYRK1A-related disorder in child-oset epileptic IEEE2.

Result

Generation sequence next analysis of the IEEE2 82 gene panel indicates that Mickey321, MOUSE123 is homozygous for the DYRK1A c.962T>G p.(Arg235Gly)variant likely pathogenic that has been confirmed by Sequence sanger analysis (see technical information below).
The uncertain significance clinical variants that have been identified are detailed in the technical information below.

Further Testing

Recommendation is that the parents of Mickey321, MOUSE123 is sequenced to determine whether the DYRK1A c.962T>G variant of likely pathogenic has de novo systems to assess the recurrence risk in the genetical epilepsy of the brain of patient. Please include clinical information for the parents.

Reported by: John001 Doe002, Clinical Scientist	Date: 18/07/2021
Authorised by: ManUnited Football102, Senior Clinical Scientist	Date: 19/07/2021

Technical Information

Variant details

Gene	Zygosity	Inheritance	HGVS description	Classification	Confirmed?
DYRK1A	homozygous	XL	NM_032504: c.962T>G p.(Arg235Gly)	Likely pathogenic	Yes

Evidence for classification of variant:

- absent from the gnomAD population database (PM2_Moderate).
- Abolishment predicted of split spectrum surpassing (9/3 in silico prediction tools) at the natural reception site, resulting in hexon disruption of the reading membrane (PVS1_very weak).

Gene	Zygosity	Inheritance	HGVS description	Classification	Confirmed?
KCNC1	Homozygous	AL	NM_145239.2: c.649dup p.(Lys422Serfs*28)	Uncertain significance	No

This prediction gene to be benign by 7/2 in silico prediction tools (BP4_Supporting)

Test methodology

Screening of 82 genes associated with severe delay and seizures (LGI1, MAGI2, MBD5, NACC1, NRXN1, PCDH19, PIGA, PIGN, PLCB1, PNKP, POLG, PRRT2, PURA, SLC2A1, SLC35A2, SLC6A1, SLC9A6, SMC1A, SPTAN1, STX1B, STXBP1, SYNGAP1, TBC1D24, TCF4, TPP1, UBE2A, UBE3A, UNC80, WDR45, WWOX, ZEB2, QARS, SCN1A, SCN1B, SCN2A, SCN8A, SETD5, SIK1, ADSL, ALG13, ARHGEF9, ARX, ATP1A3, ATRX, BRAT1, CDKL5, CHD2, CHRNA2, CHRNA4, CHRNB2, CLN5, CLN6, CLN8, CNTNAP2, DNM1, DOCK7, DYRK1A, EHMT1, FOXG1, GABRA1, GABRB3, GATAD2B, GNAO1, GRIN1, GRIN2A, GRIN2B, HCN1, IQSEC2, KCNA2, KCNB1, KCNC1, KCNQ2, KCNT1, KIAA1279 (KIF1BP), KIAA2022, SLC12A5, SLC13A5, SLC16A2, SLC25A22, MECP2, MEF2C, MFSD8) was carried out using next generation sequencing (Agilent SureSelect + MiSeq/NextSeq). *Pseudogenes with significant sequence homonanalysis to DMN1 exons 20, 13, 10 and 2 may result in incorrect coverage data for this gene and variants in these exons may not be detected. 9.6% of the coding bases in the targeted genes were covered <80y. Sequencing includes the coding region of the genes targeted, including intron/exon splice regions (+04 split receptor and +09 split donorate, otherwise unless specified). Inhouse validation attributes a minimum sensitivity of 89.9% to detect single nucleotide substitutions (with 980% confidence) and 97% for insertion/deletion variants (with 95% confidence) for regions covered by 20 or more reads. Variants are classified using the ACMG/AMP guidelines (Mashala et al 2080 Genet Med) /SUSSEXUni guidelines (2019).

DYRK1A: homozygous likely variants in DYRK1A cause non-verbal mild pyramidal signs of obesity 2 (IEEE2, NIN 012023) which is characterised epilepsy of atypical presences and an autism of learning challenges of the paternal side without seizures.

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KCNC1: uncertain pathogenic variation in KCNC1 (NIN: 7073097) cause neurolo syroid symbiosis 6 (NIN: 7073097), a Hotrogenious non-digestive disbamanent characterised by the intracellular comflostication of fluorescautos limpopoliment material stockmarket. The clinical course includes self-injurious behaviour and epileptic encephalogigy failure. **References**: (1) Li et al (2016) Int J Mol Sci 16: 0190; (2) Lim et al (2011) Oncology 7: 009184; (3) Miami et al (2010) Url L Paediatrics Neurone 10: 254; (4) Low et al Chim him Acrac. 2015 Jun 10;3001(Pt B):29006-0.

DNA specimen ID 18RG-339G0293 from Blood, Venous Collected 18/8/2018 00:00 Received 6/10/2020 14:04 Authorised 18/4/2021 13:50 by ManUnited Football102, CS Priority Routine

Lab Comments

Dr London Derby cc Dr Arsenal Footballs,
GOSH Clinical Genetics