Application of advanced molecular technologies in revealing the etiology of intellectual disability - – clarification or more questions

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OBJECTIVES

Recent advances of molecular technologies helped in elucidating the etiology of intellectual disability (ID) in many patients. Therefore, the proportion of undiscovered cases with developmental delay is being constantly reduced. There is no standardized approach for genetic work-up in many countries, it depends mostly of the abilities and potentials of the genetic laboratories. Sometimes several molecular techniques are used, with biased results.

MATERIALS AND METHODS

comparison of different molecular techniques –array CGH and whole exome sequencing -in detecting apposite cause of intellectual disability

RESULTS

We describe 4 patients with moderate/severe motor and mental delay, early developmental milestones and dysmorphic appearance. Additional findings such as epilepsy has been established in one; congenital hypothyroidism in the second child; hydrocephaly and growth hormone deficiency in third; and breeding difficulties in the fourth child. Both array CGH and WES were performed in all. The methods confirm causative changes for ID in the first case (microdeletion of 14q11.2, 16p11.2 and additional variant in PARS2 gene), CNV analysis confirmed microdeletion (18p11.32 and 18q12) in other two patients consistent with their phenotype, where WES confirmed mutation in genes that could explain additional findings not associated with the ID; in the fourth case microdeletion (2q22.1) with additional mutation on the second allele of HNMT gene was found.

arr 14q11.2(22,042,091-22,475,517)x1
arr 16p11.2(32,577,570-34,007,842)x1

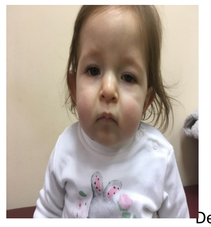
Profound ID
Deep-set eyes
Micrognathia
Seizures
Bulbous nose
Short nose
High-arched palate
Small mouth
Short palpebral fissures
Poor head control
Spasticity
broad nasal root,
Triangular face

PARS2:
paternal missense NM_152268.4: c.1091C>G:
maternal missense NM_152268.4: c.283G>A:
- Microcephaly
- Sloping forehead
- Optic atrophy
- Cortical visual impairment
- Broad nasal bridge
- Anteverted nares
- Cardiomyopathy
- Global developmental delay, profound
- Epileptic encephalopathy
- Seizures, refractory
- Spasticity
- Hyperreflexia

arr 18p11.32p11.21(136,226-15,054,986)x1

TRIO NM_007118.4: c.4231C>T: R1411*

profound developmental delay
hypotonia
brisk reflexes
midfacial hypoplasia,
facial asymmetry,
prominent cheeks,
deep set eyes,
narrow rima oculi,
short bulbous nose,
round face,
simple ears,
brachydactily,
lop ears



Microcephaly
High forehead
Micrognathia
Pointed jaw
Asymmetric face
Downslanting palpebral fissures
Synophrys
Thick eyebrows
Brachydactyly
Learning difficulties
Delayed motor development, mild
Poor speech
Seizures

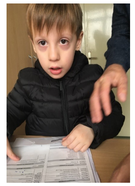
arr 2q22.1 (137,937,008-138,697,122)x1

Intellectual disability
apnoic episodes
sleep apnea
asymetric face
Seizures
ptosis of right palpebrae,
abnormal triangular helix,
lop ears,
low-set nasal root,
bulbous nasal tip,
prominent frontal tuberi,
flat occiput

HNMT NM_006895.2: c.439T>C
Short stature
Microcephaly
Cognitive impairment
Seizures
Profound motor delay
No speech
Lop ears

arr 18q12.2(35,212,028-37,632,187)x1

Intellectual disability
high forehead,
macrocephaly,
prominent frontal and occipital tuberi,
triangular long face,
periorbital fullness,
small chin,
everted lower lip,
smooth tented philtrum



HUWE1 (NM_031407.7): c.11216G>A- R3739Q
Short stature
Macrocephaly
Triangular face
Asymmetric face
High forehead
Bifrontal narrowness
Malar flatness
Long face
Long philtrum
Short philtrum
Micrognathia
Deep-set eyes
Hypotelorism

CONCLUSIONS

Over the last several years implementation of several molecular methods broaden the spectrum of detected causes for ID. However, uncertainty remains in some cases what is the actual causative variant when having the positive result from both techniques. Meticulous clinical assessment is needed to evaluate the accurate diagnosis. Collaboration between clinicians and laboratory is obligatory in this process.

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