

Case Report

Further Example of Classical Autism Patient Associated to *PTCH1* Gorlin Syndrome

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- Secondary findings

Abstract

We report on the second case of a classical autistic patient carrying a *PTCH1* Gorlin syndrome mutation (c.3281_3282dupTG; p.Glu1095Trpfs*12) identified through a neurodevelopmental panel by next generation sequence. Clinical review of the patient revealed typical Gorlin nevoid basocellular syndrome with macrocephaly, palmar/plantar pits, and calcification of the cerebral falx. There is evidence for an underlying neurodevelopmental disorder in autistic patients; and, links between hedgehog morphogen through *PTCH1* receptor has recently been investigated revealing changes in brain morphology in children with nevoid basal cell carcinoma syndrome. This report further links Gorlin syndrome phenotype and *PTCH1* mutations to the autism spectrum disorder scenario. Recommendations regarding primary prevention and surveillance are discussed.

INTRODUCTION

Autism is characterized by qualitative impairments in reciprocal social interactions and communication coupled with restricted and stereotyped patterns of interests and activities. Although described in terms of social and behavior abnormalities autism is also associated with an uneven pattern of cognitive defects. Only a small percentage of children with autism have a specific genetic diagnosis and in 90% of the cases the cause remains unknown. On the other hand, Gorlin syndrome, known as basal cell nevus syndrome, is an autosomal dominant condition caused by mutations in the tumour suppressor gene *PTCH* which functions as a receptor for hedgehog. We report on the association of autism spectrum disorder in a patient with cleft lip and macrocephaly who revealed a mutation in the *PTCH1* gene. Clinical review of the patient showed clearly a typical non-familial case of Gorlin syndrome. A previous case of autism and Gorlin syndrome has been documented in an 8.9 years old girl [1].

CASE STUDY

A male patient was referred for evaluation due to global developmental delay and cleft lip/palate at 3.4 years of age (Figure 1). The patient was born from non-consanguineous parents, GESTA II PARA II. He has a normal younger brother. His birth was unremarkable weighting 3.070g and 51 cm in length. At birth a left cleft lip/palate and a right pseudocleft (appearance of repaired cleft) were noted. In due time, the patient was referred

to a state reference centre for proper evaluation and repair of the clefts. He walked unaided at 18 months and had a bilateral inguinal hernia correction. No signs of other neurological problems, tantrums or convulsions were reported. The parents report that their son has an enormous ability with cell-phone and computers, including on different languages.

At physical examination, his anthropometric measurements revealed a macrocephaly (>P98) with normal length and weight for his age and family. He does not speak, evoking only sounds and noises; has an erratic behavior with “hand flapping” associated to a “pendulum” movement of the right leg always when sustained from his tiptoe walking. He has a dysmorphic face with a wide forehead and epicanthic folds; presence of fixed divergent strabism was noted; asymmetric ears and frontal whorl pattern of the hair was evident; bilateral scars on the upper lip was present; no further abnormalities was detected at that time. A cerebral MRI revealed enlarged ventricles with a Dandy Walker variant consisting of arachnoid cyst. An electroencephalogram revealed medial cortical and subcortical abnormalities characterized by complex waves with focal spikes. An otoacoustic test revealed bilateral abnormal hearing. A conventional karyotype and CGH-array (180K) was normal.

Whole Exome Sequence (WES) was performed through Next era Exome Capture and Illumina HiSeq new generation sequence and analysed through GRCh37 human genome reference; and, revealed a pathogenic mutation in the *PTCH1* gene - c.3281_3282dupTG; p.Glu1095Trpfs*12 - promoting substitution



Figure 1 (a) patient at age 5.3y; (b) plantar pits; (c) Calcification of cerebral falx (arrow).

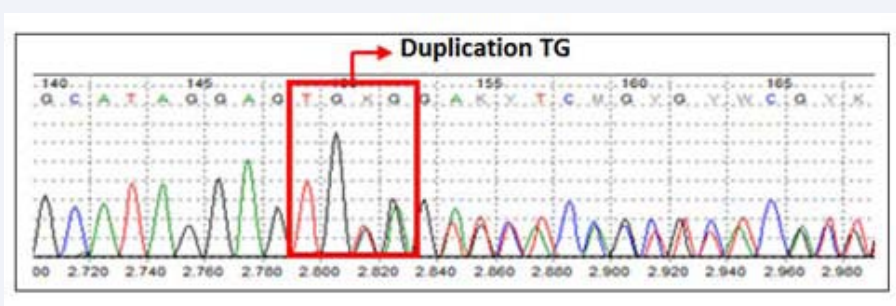


Figure 2 Electropherogram of patient's *PTCH1* mutation - c.3281_3282dupTG; p.Glu1095Trpfs*12 promoting substitution of glutamate at position 1095 for tryptophan with change of the framework introducing a stop codon that truncated the protein reading.

of glutamate at position 1095 for tryptophan with change of the framework introducing a stop codon that truncated the protein reading (Figure 2).

Clinical re-evaluation of the patient at 5.3 years, the following clinical features were present based on the assumption that Gorlin basocellular syndrome (OMIM 109400) [2] was the patient's final diagnosis: macrocephaly (P>98); hand/feet plantar pits (Figure 1b); calcification of the cerebral falx (Figure 1c); absence of ribs abnormalities on thorax X-ray scan; absence of skin abnormalities; absence of meningioma on a recent cerebral MRI; and, absence of odontogenic cysts. No formal neurodevelopmental testing was performed for the autism spectrum disorder.

DISCUSSION

WES investigation in autism has been widely indicated for clinical purposes and an overall review including genetic linkage data, candidate genes and genome-wide association studies along with further advances in genetic technology high resolution DNA microarray and next generation sequencing included have led to a compilation of 629 clinically relevant candidate and known genes for ASD [3]. Furthermore, SFARI Simons Foundation Autism Research Initiative updated to 881 genes with annotations and links to publish papers. Of these 23 genes are considered high confidence genes and further 42 considered strong candidates genes.

To the best of our knowledge, *PTCH1* mutation associated to autism has been only previously reported in an 8.9 years

Belgium girl suspected as Gorlin syndrome due to macrocrania, hypertelorism and epidermal punctiform lesions in the palm of the hand; and, molecularly confirmed the diagnosis by finding a deletion of 22 base pairs in the *PTCH1* gene [1]. In our patient, the finding of a c.3281_3282dupTG mutation in the *PTCH1* gene was unexpected due to the overwhelming clinical presentation of the case from a neurodevelopmental and ASD viewpoint. Typical autism behavior with all rituals of stereotyping movements of arms and legs, series of sounds and noises with tiptoe walking indicated the clinical diagnosis in favour of autism. The presence of cleft lip/palate and a pseudocleft of the lip increased the diagnostic predictive value for a chromosome abnormality that proved otherwise normal by CGH-array analysis.

The diagnosis of Gorlin syndrome in our patient became straight forward comprehending two major criteria's such as lamellar (sheet-like) calcification of the falx and palmar/plantar pits; and, two minor criteria's as macrocephaly and cleft lip/palate. Multiple basal cell carcinomas, medulloblastoma and vertebral/ribs anomalies were formerly investigated and excluded.

The genomic result in our patient could be considered a secondary finding (SF) since the mutation found comprises and would be more appropriate as part of the hereditary cancer syndromes instead of ASD group. Over this matter, the ACMG board stated in 2016: "...*PTCH1* associated with Gorlin syndrome/nevoid basal cell carcinoma syndrome, did not achieve a consensus among the Secondary Findings Maintenance Working

Group as for addition in the list of 59 medically actionable genes recommended for return in clinic genomic due to insufficient evidence that knowledge of a known pathogenic/expected pathogenic variant in the gene would alter medical management [4]. Such diagnosis in a young boy with Gorlin syndrome makes us wonder if anticipation of clinical monitoring for complications such as multiple basal cell carcinomas/medulloblastoma would indeed may support inclusion of this SF as a medically actionable gene; in such a way, that appropriate skin protection can be recommended; and, furthermore, genetic counselling achieved for parents.

Prevention and surveillance of primary manifestations in affected Gorlin syndrome individuals should be considered in several aspects. Awareness of the risk of medulloblastoma and other clinical complications for Gorlin children patients in the first years of life is important and may justify clinical assessment and physical examination in a routine basis [5]. For children, head circumference should be followed throughout childhood. Rapid enlargement should prompt evaluation for possible hydrocephalus. This may include, orthopantogram every 12-18 months in individuals older than age eight years to identify jaw keratocysts, and skin examination at least annually. Radiotherapy should be avoided if there are alternative treatments, especially in childhood such as investigative radiology [6]. Asymptomatic

older and younger at-risk relatives (including children) of an affected individual would benefit as well from surveillance for complications of Gorlin syndrome.

REFERENCES

1. Delbroek H, Steyaert J, Legius E. An 8.9 year old girl with autism and Gorlin syndrome. *Eur J Paediatr Neurol.* 2011; 15: 268-270.
2. OMIM®Online Mendelian Inheritance in Man® an Online Catalog of Human Genes and Genetic Disorders. 2018.
3. Butler MG, Rafi SK, Hossain W, Dietrich A, Stephan DA, Manzardo AM. Whole Exome Sequencing in Females with Autism Implicates Novel and Candidate Genes. *Int J Mol Sci.* 2015; 16: 1312-1335.
4. Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med.* 2017; 19: 249-255.
5. Foulkes WD, Kamihara J, Evans DGR, Brugières L, Bourdeaut F, Molenaar JJ, et al. Cancer Surveillance in Gorlin Syndrome and Rhabdoid Tumor Predisposition Syndrome. *Clin Cancer Res.* 2017; 23: 62-67.
6. Evans DG, Birch JM, Orton CI. Brain tumours and the occurrence of severe invasive basal cell carcinoma in first degree relatives with Gorlin syndrome. *Br J Neurosurg.* 1991; 5: 643-646.

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