

Table 1 Health areas with the highest coverage rates for the PCV13 vaccine in the ACV, and percentage of children that did not belong to any risk groups.

Area	Third dose			Children not at risk	
	N	Coverage (%)	95% CI	N	%
A	62	68.9	58.2–79.6	60	96.8
B	169	59.7	53.7–65.7	167	98.8
C	211	49.3	46.8–51.8	195	92.4
D	220	55.2	52.6–57.7	210	95.5
Total	662	–	–	632	95.9

ACV, Autonomous Community of Valencia; CI, confidence interval.

In these health areas, 91.9% of the third doses were not supplied by the public health system, so we assume that these doses were purchased at pharmacies by parents.

The total expenditure in third doses for children that did not belong to any risk group in the ACV amounted to 158 176.48€, of which 43 304.80€ corresponded to the Valencian Public Health System for vaccination events that were covered under the tax laws⁵ of the Government of the ACV.

The PCV13 vaccine coverage rate in the ACV in 2014, before the vaccine was included in the routine immunization schedule, was 67%,⁴ which already sufficed to achieve herd immunity. Therefore, a third dose at age 6 months is not justified by the vaccination coverage rates either before or after the inclusion of the PCV13 vaccine in the routine schedule, save in children belonging to risk groups.

High coverage rates have been achieved since the PCV13 vaccine was first included in the routine immunization schedule, so a third dose at 6 months would not be indicated except in at-risk children. The additional and inefficient costs for both parents and the Department of Public Health are considerable. When it comes to vaccination, more is not always better, so we must apply the best and most efficient scientific evidence that is currently available for the benefit of the population and immunization programmes.

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New genetic mutation associated with Pierson syndrome[☆]



Nueva mutación genética asociada con el síndrome de pierson

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Dear Editor:

We present the case of a female newborn, unremarkable pregnancy, born at term. Low birth weight for gestational age. Parents were first cousins, originally from Pakistan, with two previous healthy sons. On initial examination she was found to have bilateral megalocornea and microcoria.

During her first week of life, she developed lethargy, oxygen desaturations and bradycardia. Blood tests showed severe metabolic acidosis (pH 7.17, PCO₂ 51 mmHg, HCO₃ 18.6 mmol/L, BE – 9 mmol/L) with hypoproteinemia, hypoalbuminemia (total protein 2.8 g/dl, albumin 1.4 g/dl) and increased creatinine (1.03 mg/dl). Urine tests showed

proteinuria (nephrotic range – 600 mg/dl). A brain MRI showed mild periventricular white-matter signal alterations. These findings, added to the ocular malformations, raised the suspicion of Pierson syndrome (PS).

The patient was managed symptomatically. Despite supporting measures, she developed progressive renal failure (maximum creatinine 3.07 mg/dl and urea 142 mg/dl), with multiple acid–base and electrolyte disorders, anemia and uncontrolled systemic arterial hypertension.

At the age of two months, she progressed to cardiogenic shock that did not respond to medical treatment. Due to the clinical course of the disease and the dismal prognosis, withdrawal of life support was agreed, with the patient dying within several hours.

Genetic testing was performed on our patient. A blood sample in K3-EDTA was obtained, and DNA from lymphocytes was extracted for molecular studies. Amplified DNA fragments of the 32 coding exons and flanking intronic regions of the LAMB2 gene were obtained by PCR. These were subjected to mutational screening by direct sequencing using an Applied Biosystem® 3500 DX Genetic Analyzer, and compared to the consensus sequence of the transcript NM_002292.3. A suspected homozygous variant c.1405+2dupT in the intron 10 of the LAMB2 gene was detected (subsequently confirmed by finding the same mutation in heterozygosis in both parents). This mutation has not been previously described as a polymorphism or associated with PS in the databases searched (HGMD®, LOVD, ExAC browser and 1000 genomas). However, this mutation could affect the splice donor site in intron 10, producing an aberrant splicing and a malfunctioning protein.

PS is a rare and fatal autosomal recessive disorder. Characteristic findings include congenital nephrotic syndrome and ocular malformations. It is due to mutations in the LAMB2 gene, found in chromosome 3p21, which encodes laminin-beta-2 protein. Laminin-beta-2 is expressed in the glomerular basement membrane, where it plays a role in anchoring and differentiation of podocyte foot processes.¹ If this membrane integrity is lost, massive proteinuria and hypoalbuminemia develops, leading to end-stage renal disease and, in most cases, death in the first months of life. Laminin-beta-2 is also found in the connective tissue of ocular and nerve structures, causing a broad range of ocular and neurologic impairment.

There are currently 52 known mutations associated with PS (HGMD®). Some of the known mutations in the LAMB2 gene have genotype/phenotype correlation. Different mutations have been described – some predict a total loss of function of the protein while others lead to some remaining function.^{2–4} The mutation found in our patient has not been previously described, neither as polymorphism nor as associated with PS. The bioinformatic predictors Mutation T@sting and Human Splicing Finder report that this mutation most probably affects the splicing region in intron 10 of LAMB2, predicting an aberrant splicing and a malfunction of the protein laminin-beta-2. Moreover, pathogenic mutations in c.1405+1G>A⁵ and c.1405+3A>T⁶ have already been reported, which would affect the same splicing region as the mutation in our patient, supporting its pathogenicity.

In autosomal recessive (AR) diseases de novo mutations are rare, and there are normally no manifestations of the disease in heterozygous individuals. If we consider this mutation as potentially pathogenic, taking into account the AR inheritance of the disease, the presence of this mutation in homozygosis is most probably the cause of the disease in our patient.

In these diseases, knowing the genetic cause of the disease is important to be able to establish the risk of recurrence, offer appropriate genetic counseling and options to prevent recurrence in a family. In AR diseases, where both parents are healthy carriers, the risk of recurrence is 25%.

To confirm the pathogenicity of this mutation, further case reports of patients with PS and this same mutation should be reported as well as functional assays which are not always available. If this is confirmed, it is probable that this specific mutation is associated with a severe phenotype as our patient's disease had neonatal-onset, with ocular, renal and neurologic findings and has had a dismal outcome at the age of two months.

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