Homozygous EXOSC3 Mutation c.92G→C, p.G31A is a Founder Mutation Causing Severe Pontocerebellar Hypoplasia Type 1 Among the Czech Roma

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Abstract: Pontocerebellar hypoplasia type 1 (PCH1) is characterized by cerebellar and anterior horn motor neuron degeneration and loss, signs of spinal muscular atrophy plus. Patients manifest severe perinatal weakness, hypotonia, and respiratory insufficiency, causing death frequently before the age of 1 year. Recently, causative mutations in EXOSC3 were reported in a majority of PCH1 patients, but the detailed clinical phenotype caused by EXOSC3 mutations, genotype-phenotype correlations, and prevalent mutations in specific ethnic groups is not yet known.

Three unrelated Czech Roma patients with PCH1 were investigated clinically, electrophysiologically, neuroradiologically, and neuropathologically (patients 1 and 2). The entire coding region of the EXOSC3 gene, including the adjacent intron sequences, was sequenced in all three patients. The same mutation c.92G→C, p.G31A in EXOSC3 was found in all three affected patients in homozygous state and in heterozygous state in the parents from two of the families. Haplotype analysis with four flanking microsatellite markers showed identical haplotype in 9 out of 11 haplotypes carrying the c.92G→C, p.G31A mutation. Furthermore, four heterozygotes for this mutation were found in anonymous DNA samples from 90 unrelated Roma individuals. All four of these samples shared the same haplotype. No heterozygous sample was found among 120 anonymous DNA samples from Czech non-Roma individuals with no familial relation. It may therefore be concluded that EXOSC3 c.92G→C, p.G31A mutation is a founder mutation with high prevalence among the Czech Roma causing a similar and particularly severe phenotype of PCH1. These observations from the Czech Roma may have consequences also for other Roma from other countries.

PCH1 caused by EXOSC3 founder mutation c.92G→C, p.G31A extends the list of autosomal recessive disorders rare among the general population but more frequent among Roma at least in the Czech Republic.

Keywords: pontocerebellar hypoplasia type 1, olivopontocerebellar hypoplasia, Roma, Romanies (gypsies), spinal muscular atrophies of childhood

INTRODUCTION

Spinal muscular atrophy (SMA) plus syndromes are infantile variants of SMAs with additional or atypical features (Kizilates et al., 2005). SMA plus includes SMA with respiratory distress (SMARD [OMIM 604320]); infantile lethal X-linked SMA with arthrogryposis and congenital fractures (SMAX2 [301830]); SMA with arthrogryposis and bone fractures (OMIM 271225); and SMA with pontocerebellar hypoplasia (PCH), also known as PCH type 1.
(PCH1A [OMIM 607596]; PCH1B [614678]) (Renbaum et al., 2009).

The combination of PCH and anterior horn cells loss was first described by Norman (1961) and was reviewed by Chou et al. (1990), Barth (1993), and Namavar et al. (2011b).

PCH1 is clinically characterized by congenital and severe hypotonias, severe muscle weakness, areflexia, and, frequently, early respiratory insufficiency. At birth, multiple congenital contractures of large joints may be present. Severe mental retardation and cerebellar signs such as nystagmus and ataxia follow the initial manifestation (Barth, 1993; Chou et al., 1990; Namavar et al., 2011b; Szabo et al., 2008). Life expectancy among PCH1 patients is severely shortened, and death is frequent before the age of 1 year. Postmortem studies revealed a variable spectrum of cerebellar hypoplasia or atrophy, and neuronal loss in the anterior horns of the spinal cord, basal ganglia, and brainstem (Barth, 1993; Barth et al., 2007; Goutieres et al., 1977; Namavar et al., 2011b; Norman, 1961).

Inheritance of PCH1 is autosomal recessive and may be mistaken for severe infantile SMA (Rudnik-Schoneborn et al., 2003; Rudnik-Schoneborn et al., 1995).

Linkage to chromosome 5q markers has been excluded in some families, confirming genetic heterogeneity between infantile SMA and PCH1 (Renbaum et al., 2009; Rudnik-Schoneborn et al., 1995, 2003).

In single patients with atypical and mild PCH1 phenotype, mutations in the VRKI (encoding the vaccinia-related kinase 1 [OMIM 602168]) (Renbaum et al., 2009), RARS2 (encoding mitochondrial transfer RNA arginyl-tRNA synthetase 2 [OMIM 611524]) (Namavar et al., 2011a), and TSEN54 (encoding transfer RNA splicing endonuclease subunit 54 [OMIM 611524]) (Simonati et al., 2011) genes were reported. Recently, Wan et al. showed that the mutations in the EXOSC3 gene (encoding exosome component 3 [OMIM 606489]) are the cause of typical PCH1 in several patients from different countries (Wan et al., 2012).

The EXOSC3 gene encodes a core component of the RNA exosomes, which process and degrade RNA and thereby regulate the activity of gene expression. With this new discovery, the genetic cause of a substantial number of PCH1 patients, 30 – 40% according to Rudnik-Schoneborn et al. (2013), may be clarified, but the phenotypic spectrum of patients with EXOSC3 mutations and genotype-phenotype correlations are not known in detail. However, a first genotype-phenotype correlation study was just published (Rudnik-Schoneborn et al., 2013).

The occurrence of PCH1 in particular ethnic groups worldwide is also poorly understood. We describe three Roma patients who died early from PCH1 caused by the same EXOSC3 homozygous mutation c.92G→C, p.G31A and provide evidence that the mutation is frequent among Czech Roma and seems to be a founder mutation.

**PATIENTS AND METHODS**

Three unrelated Czech patients of Roma ethnic origin were investigated clinically, electrophysiologically (electromyography), neuroradiologically, and by DNA testing, and patients 1 and 2 were also tested neuropathologically. Patients 1 and 2 were females and patient 3 was a male. All three patients had previously undergone DNA testing of the SMN1 gene (survival of motor neuron 1 gene [OMIM 600354]); patients 1 and 2 also underwent sequencing of the VRKI gene. The Sanger method was used to sequence all four coding exons of the EXOSC3 gene, including the adjacent intron sequences. Polymerase chain reaction (PCR) primers were designed by ExonPrimer tool (http://ihg.gsf.de/ihg/ExonPrimer.html).

Ninety anonymous DNA samples from Roma individuals without known familial relationship and 120 anonymous DNA samples from unrelated non-Roma individuals were used to estimate p.G31A heterozygotes frequency in each control cohort. The p.G31A was detected by sequencing among the Roma and by restriction digest with BbvCI among non-Roma Czechs.

Four dinucleotide microsatellite (STR) markers flanking the EXOSC3 gene, namely D9S1791, D9S50, D9S1874, and D9S2148, were used for haplotype analysis in all samples where the c.92G→C, p.G31A mutation was found. Fluorescently labeled primers were used for amplification of these markers and PCR products were analyzed on ABI 3130 Genetic Analyzer (Life Technologies, Carlsbad, CA, USA).

**RESULTS**

**Clinical Findings**

The main clinical findings in all three patients are summarized in Table 1. Neuroimaging of the brains of the patients is presented in Figure 1.

Clinical phenotype and disease course and paraclinical findings were very similar in all three patients. At birth, all three patients had severe hypotonias and weakness and later experienced absent motor and mental development, lack of visual fixation, absent speech, signs of neuronal loss in spinal anterior horns, cerebellum and parts of the midbrain, progressive microcephaly, and early respiratory insufficiency leading to death by the age of 9–17 months.

**Patient Presentations—Clinical Course**

Patient 1, a female from a second uncomplicated pregnancy, was born to unrelated healthy parents, both of Roma origin, in the 38th week of gestation. Her birth weight was
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Table 1. PCH1 patients with homozygous *EXOSC3* mutation p.G31A—Clinical manifestation.

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypotonia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Moderate facial dysmorphism</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sucking difficulties</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Congenital contractures and/or polyhydramnion</td>
<td>Congenital contractures</td>
<td>Congenital contractures</td>
<td>None</td>
</tr>
<tr>
<td>Gross delay all milestones</td>
<td>No social contact, no speech, no hand and postural control</td>
<td>No social contact, no speech, weak grasping, and no postural control</td>
<td>No social contact, no speech, no hand and postural control</td>
</tr>
<tr>
<td>Progressive microcephaly</td>
<td>Yes/normal at the birth</td>
<td>Yes/normal at the birth</td>
<td>Yes/below 3rd percentile at the birth</td>
</tr>
<tr>
<td>Tongue fasciculations</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Impaired swallowing</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>Repeatedly bronchopneumonia with respiratory insufficiency</td>
<td>Death—respiratory insufficiency</td>
<td>At birth—respiratory support for 3 days; death—respiratory insufficiency</td>
</tr>
<tr>
<td>EMG—needle/peripheral neuropathy</td>
<td>Neurogenic changes/no</td>
<td>Neurogenic changes/no</td>
<td>Neurogenic changes/no</td>
</tr>
<tr>
<td>Pontocerebellar hypoplasia (CT/MRI)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Age of death/reason</td>
<td>12 months of age/respiratory insufficiency</td>
<td>9 months of age/cardiorespiratory insufficiency</td>
<td>17 months of age/respiratory insufficiency</td>
</tr>
</tbody>
</table>

2750 g (10th–25th percentiles), body length was 48 cm (10th–25th percentiles), and head circumference was 33 cm (10th percentile). Apgar scores were 9/9/9. The family history was unremarkable.

Patient 2, a female, was the third child from the fourth pregnancy (one pregnancy having been terminated after prenatal testing for hereditary hearing loss DFNB1) to unrelated Roma parents. The mother is deaf due to...

![Figure 1](image1.png)

**Figure 1.** CT and MRI examinations PCH type 1. (A–C) Patient 1: CT image at the age of 6 months. (A) Mid-sagittal, (B) coronal, and (C) transversal sections show mild cerebellar hypoplasia (*white arrows*), mild brainstem hypoplasia (*white arrowhead*), and severe vermal hypoplasia (*black arrows*) with no significant changes of ventral pons (*white arrowhead*). (D–F) Patient 2: MRI image at the age of 4 months. (D) Mid-sagittal (T2), (E) coronal (T1), and (F) transversal (T2) sections show mild cerebellar hypoplasia (*white arrowhead*), mild brainstem hypoplasia (*white arrowhead*), severe vermal hypoplasia (*black arrows*), and supratentorial mild cortical atrophy.
autosomal recessive deafness DFNB1 with homozygous mutation p.W24X of the GJB2 gene. The patient’s father is heterozygote for the same mutation and has normal hearing. Patient 2 was born at term, with birth weight of 2890 g (25th–50th percentiles), body length of 49 cm (25th percentile), and head circumference of 34 cm (10th–25th percentiles). Apgar scores were 9/9/9.

Patient 3, a male, was born from the first pregnancy to unrelated and healthy Roma parents. Birth was in the 37th gestation week by an acute cesarean section due to acute asphyxia. Respiratory support was required for 3 days. Apgar scores were 6/6/8. Birth weight was 2000 g (below the 3rd percentile), and body length was 45 cm (below the 3rd percentile). Family history was positive: one sister of his father died at the age of 3 months and her autopsy revealed severe atrophy of the cerebellum with reduced gyration. More information is not known.

In all of these patients there was no history of any potential teratogens.

Physical examination of the patients at birth was similar in all three and revealed generalized severe hypotonia, muscle weakness with areflexia, and sucking difficulties.

Over time, progressive microcephaly, severe developmental delay, generalized hypotonia with weak cry, and progressive swallowing difficulties were observed in all. Growth retardation with microcephaly was below the 3rd percentile in all. None had spontaneous antigravity movements and patient 3 had tongue fasciculation. In all three patients, vision impairment was noticeable: patients 1 and 3 could not fixate or follow with eyes, but had full range of extraocular movements with bursts of nystagmus; patient 2 was only unable to fix and follow.

Nerve conduction studies showed motor responses with severely reduced amplitudes of compound muscle action potential (CMAP), but normal sensory responses. Electromyography showed neurogenic changes and reduced interference pattern as well as high amplitudes of compound muscle action potential (CMAP), but normal sensory responses.

After magnetic resonance imaging/computed tomography (MRI/CT) of the brain showed hypoplastic or atrophic cerebellum, PCH1 was diagnosed in each patient (Figure 1).

Epileptic seizures were not noted in any of the patients.

All three patients required gastrostomy tube placement for progressive swallowing difficulties. Patient 1 died of bronchopneumonia at 12 months, patient 2 died of cardiorespiratory insufficiency at 9 months, and patient 3 died of respiratory insufficiency at 17 months in another hospital. No autopsy report is available.

Basic clinical data from patient 3 were mentioned in the paper by Wan et al. (Wan et al., 2012).

Laboratory Findings

In all three patients, extended laboratory examination was within normal ranges, including serum and cerebrospinal fluid amino acids and lactate, urine organic acids, very-long-chain fatty acids, screening for mitochondrial DNA deletions, serum and cerebrospinal fluid antibodies to toxoplasma, rubella, cytomegalovirus, and herpes simplex virus, liver panel, blood urea nitrogen and creatinine, complete blood counts, chemistries including glucose, calcium, and creatine kinase.

Neuroimaging Findings

Neuroimaging findings in all three patients on CT (patient 1) and MRI (patients 2 and 3) brain examination were very similar and included cerebellar hypoplasia, severe hypoplasia of vermis, and mild hypoplasia of the brainstem (Figure 1).

Neuropathological Findings in Patients 1 and 2

Neuropathological findings in patients 1 and 2 were very similar. The brain was small in both cases: total brain weight was 660 g (control brain weight 852 g) in patient 1 and 500 g (control brain weight 750 g) in patient 2 (Gilbert-Barness, 1997). The supratentorial structures of the brain were intact in both cases. In both cases, the cerebellar hemispheres were hypoplastic and dorsoventrally flattened. Cerebellar folia were short and exhibited poor branching. The vermis and folia were relatively spared. Microscopic examination revealed variable loss of Purkinje cells (also known as Purkinje cells) (Figure 2) and loss of neurons in granular layer in both cases (Figure 3). In patient 1, loss of the entire cerebellar cortex was occasionally found, being sharply demarcated from the surrounding cortex. Focally, in both cases, remnants of outer granular layer were found in the cerebellar cortex. Fragmentation and segmental loss of dentate nucleus with preserved islands, accompanied by gliosis, were observed in both brains. Concerning the brainstem, the ventral pons was hypoplastic in both cases and the majority of ventral pontine neurons and transverse pontine fibers were lost. Segmental loss of the inferior olivary nucleus was apparent in both cases. The medial part of inferior olivary nucleus was more affected, being accompanied by gliosis (Figures 4 and 5).

Profound loss of motor neurons in the spinal anterior horns was apparent in both cases and was accompanied by reactive gliosis. Consequently, the striated muscle showed neurogenic atrophy with fiber type grouping. No signs of myopathy or other structural changes were seen in muscle analysis. Examination of the peripheral nerve revealed no abnormality.
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Genetic Findings

Initial DNA testing of all three patients showed two copies of the SMN1 gene. Sanger sequencing did not find any mutation in the coding region of the VRK1 gene in patient 1 or 2. After the recent clarification of the cause of PCH1 by mutations in the EXOSC3 gene, the entire coding region of the EXOSC3 gene was sequenced and revealed the same mutation c.92G→C, p.G31A in homozygous state, subsequently in all three patients and in heterozygous state in the parents of patients 1 and 2. The parents of patient 3 were not available for testing. A DNA sample from an unborn sibling whose fetus was aborted after prenatal diagnosis in family 2 and homozygous mutation p.W24X in the GJB2 gene was subsequently tested for the EXOSC3 mutation. The fetus was also homozygote for the mutation c.92G→C, p.G31A.

Testing of 90 anonymous DNA samples from unrelated Roma revealed, surprisingly, four heterozygotes (4.4%). In the control group of 120 anonymous DNA samples from unrelated Czech non-Roma individuals, no heterozygote was detected. These 11 haplotypes were then analyzed; four heterozygotes for mutation c.92G→C, p.G31A detected among the anonymous Roma controls (four haplotypes); three homozygotes for mutation c.92G→C, p.G31A in PCH1 patients (six haplotypes); and one compound heterozygote for mutation c.92G→C, p.G31A from the heterozygous mother of two patients from the family reported earlier in Wan et al. (2012).

Nine out of 11 reconstructed haplotypes in seven out of eight individuals were identical (178-90-195-150), one almost identical (178-90-197-150), and one haplotype completely different (174-94-191-150) (Table 2).

Figure 2. Purkinje (also known as Purkinje) cells (arrowheads) are only focally preserved in the hemispheric cerebellar cortex in patient 2. Hematoxylin and eosin stain, magnification 200×. Scale bar = 200 μm.

Figure 4. Inferior olivary nucleus (arrows) of the patient 1, with the medial leave of the olivary nucleus (arrowheads) being more affected by neuronal loss. Hematoxylin and eosin stain, magnification 20×. Scale bar = 1000 μm.

Figure 3. Segmental loss of internal granular layer (arrows) in the cerebellar hemispheres in the patient 1. Hematoxylin and eosin stain, magnification 100×. Scale bar = 200 μm.

Figure 5. Segmental neuronal loss of the inferior olivary nucleus. Scattered neurons are preserved within the area of the olivary nucleus (arrowheads). Hematoxylin and eosin stain, magnification 100×. Scale bar = 200 μm.
Table 2. Haplotype analysis of EXOSC3 region.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Physical distance (kB)</th>
<th>Genetical distance (cM)</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
</tr>
</thead>
<tbody>
<tr>
<td>D9S50</td>
<td>982.2</td>
<td>60.59</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>D9S1874</td>
<td>562.7</td>
<td>61.38</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>EXOSC3</td>
<td>0</td>
<td>63.65</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>D9S2148</td>
<td>510.8</td>
<td>63.65</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>


Haplotype analysis with four STR markers flanking the EXOSC3 gene. Haplotypes were constructed and compared with each other for all samples where the c.92G→C, p.G31A mutation was detected.

Identical risk haplotype is marked with gray shading. Alleles linked with the pathogenic mutation (“C”) are in bold. Identical haplotypes 178-90-195-150 were detected in 9 out of 11 haplotypes containing the p.G31A mutation. In one further haplotype, there is a small difference of 2 bp in one marker (the other three alleles are identical) 178-90-197-150. This may be caused by a mutation or a recombination.

In one sample, namely in patient 2 and her father, the p.G31A mutation is on a completely different haplotype, 174-94-191-150, which may be explained by a reciprocal recombination event in previous generations.

DISCUSSION

PCH1 is a severe disorder with prenatal onset. Several cases diagnosed with PCH1 were reported before the recent discovery of the EXOSC3 causative gene. Recessive mutations in VRK1, TSEN54, and RARS2 were reported in a few individuals with rather atypical phenotype. Recently Wan et al. (2012) reported mutations in EXOSC3 as the cause of PCH1 in 14 of 19 patients (9 families from 13 families) with infantile spinal motor neuron disease, cerebellar hypoplasia or atrophy, progressive microcephaly, and profound global developmental delay. We clinically diagnosed PCH1 in three unrelated Czech patients, all of Roma ethnic origin. All three had the same and recently reported mutation c.92G→C, p.G31A in EXOSC3 in homozygous state.

Homozygous ancestral mutations are known to cause several other monogenic, also autosomal recessive, disorders among Roma (congenital cataracts, facial dysmorphism, and neuropathy [OMIM 604168]; congenital myasthenic syndrome [OMIM 608931]; hereditary motor and sensory neuropathy Lom type [OMIM 6014551]; autosomal recessive deafness 1A, 1B [OMIM 220290, 612645]). No familial relation between the families of the three patients was detected and all three have different last names and live in different regions of the Czech Republic.

The Roma are a transnational minority originating from a limited founder group of individuals from India. Similarly to other genetically isolated founder populations, the Roma have a number of unique rare autosomal recessive disorders (Navarro & Teijeira, 2003).

Homozygotes for EXOSC3 missense mutation p.Asp132Ala have milder phenotype and much longer survival. Our patients, also homozygotes for missense mutation, have severe phenotype, which is very similar in all three patients. This may suggest a closer correlation between phenotype and this genotype. Compound heterozygotes for p.G31A and W238R also have severe clinical manifestation.

The family of patient 2 is illustrative of the high risk of recessive disorders that threaten the Roma. This family is affected by two different autosomal recessive disorders: PCH1 and nonsyndromic deafness DFNB1. A DNA sample of the aborted fetus, stored because of the prenatal finding of the homozygous mutation p.W24X of GJB2 gene, was subsequently tested for the EXOSC3 c.92G→C, p.G31A mutation. The fetus was found to be homozygous also for this mutation.

No earlier work has reported a higher incidence of PCH1 in one ethnic group. We found a surprisingly high frequency of the c.92G→C, p.G31A mutation in the Roma population from the former Czechoslovakia, namely, 4.4% (4 homozygotes among 90 anonymized DNA samples). The same mutation was not found among 120 anonymous DNA samples from unrelated Czechs of non-Roma
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origin. We are aware that this very high frequency of c.92G→C, p.G31A heterozygotes in Roma controls may be influenced by the small and limited number of samples tested. Even half of this frequency (2 out of 90), however, is surprisingly high and it is quite difficult to collect a larger control sample cohort with this ethnicity. EXOSC3 c.92G→C, p.G31A mutation causing PCH1 seems to be another ethnically specific mutation threatening the Roma population, at least in the Czech Republic, but it may have important consequences also for other Roma in Europe. If the heterozygous frequency among Roma were 4.5%, the expected frequency of homozygotes would be 1:2000 (5/10,000) or even half the carrier frequency, i.e., 2.25%, the expected frequency would still be more than 1:10,000 (1.26/10,000). Offering Roma couples a test for this ancestral EXOSC3 mutation during preconception genetic counseling therefore seems to be advisable.

CONCLUSION

We have presented three patients with a particularly severe and similar PCH1 phenotype caused by the same homozygous mutation c.92G→C, p.G31A in the EXOSC3. We provide strong evidence that p.G31A is a founder mutation and is frequent among Roma in the Czech Republic. This mutation extends the list of autosomal recessive mutations threatening the Roma in the Czech Republic and may be also in other countries. Our findings of three patients with PCH1 caused by EXOSC3 mutations confirm the recent Wan et al. discovery that the EXOSC3 gene is the causative gene in the substantial part of patients with PCH1 (Wan et al., 2012). Discovery of mutations in the EXOSC3 gene now enables molecular confirmation of previously diagnosed patients who are frequently no longer alive and enables targeted genetic prevention as prenatal or preimplantation genetic diagnosis in affected families.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

This work was Supported by a project for conceptual development of research organization 00064203 and by IGA MH CR NT 14348.

REFERENCES


Namavar, Y., Barth, P. G., Poll-The, B. T., & Baas, F. (2011b). Classification, diagnosis and potential mechanisms in pontocerebellar hypoplasia. Orphanet J Rare Dis, 6, 50.


