

# Neu-Laxova Syndrome, an Inborn Error of Serine Metabolism, Is Caused by Mutations in *PHGDH*

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Neu-Laxova syndrome (NLS) is a rare autosomal-recessive disorder characterized by severe fetal growth restriction, microcephaly, a distinct facial appearance, ichthyosis, skeletal anomalies, and perinatal lethality. The pathogenesis of NLS remains unclear despite extensive clinical and pathological phenotyping of the >70 affected individuals reported to date, emphasizing the need to identify the underlying genetic etiology, which remains unknown. In order to identify the cause of NLS, we conducted a positional-mapping study combining autozygosity mapping and whole-exome sequencing in three consanguineous families affected by NLS. Surprisingly, the NLS-associated locus identified in this study was solved at the gene level to reveal mutations in *PHGDH*, which is known to be mutated in individuals with microcephaly and developmental delay. *PHGDH* encodes the first enzyme in the phosphorylated pathway of de novo serine synthesis, and complete deficiency of its mouse ortholog recapitulates many of the key features of NLS. This study shows that NLS represents the extreme end of a known inborn error of serine metabolism and highlights the power of genomic sequencing in revealing the unsuspected allelic nature of apparently distinct clinical entities.

Neu-Laxova syndrome (NLS [MIM 256520]) is a term coined by Lazjuk in 1979 to unify the independent reports by Neu and Laxova on a lethal multiple-congenital-anomaly syndrome.<sup>1–3</sup> The main features of NLS involve defective somatic growth and CNS and skin development, in addition to many other anomalies that might represent primary malformations or a malformation sequence. Growth restriction is a constant feature that is usually apparent in the second trimester, and it could be argued that NLS could be classified as a primordial dwarfism disorder, especially given that frank skeletal dysplasia is uncommon in this condition.<sup>4</sup> Another constant feature is abnormal brain development, most commonly in the form of profound microcephaly; a head circumference of 20 cm at term has been reported.<sup>5,6</sup> Most of the case reports that describe detailed brain examination by imaging or on autopsy converge on a highly characteristic phenotype of the brain. In addition to being extremely small in volume, the brain has a distinctive pattern of lissencephaly, which some label as lissencephaly type III to differentiate it from type I, seen in Miller-Dieker syndrome (MIM 247200), and the cobblestone type II, seen in Walker-Warburg syndrome (MIM 236670) and related disorders of glycosylation. The cerebellum is often hypoplastic, and complete absence of the vermis has frequently been reported. In addition, the corticomedullary tracts are often small or absent in the brainstem and spinal cord.<sup>5</sup> It has been proposed that in view of the severity of CNS involvement, the skeletal manifestations in the form of contractures and syndactyly

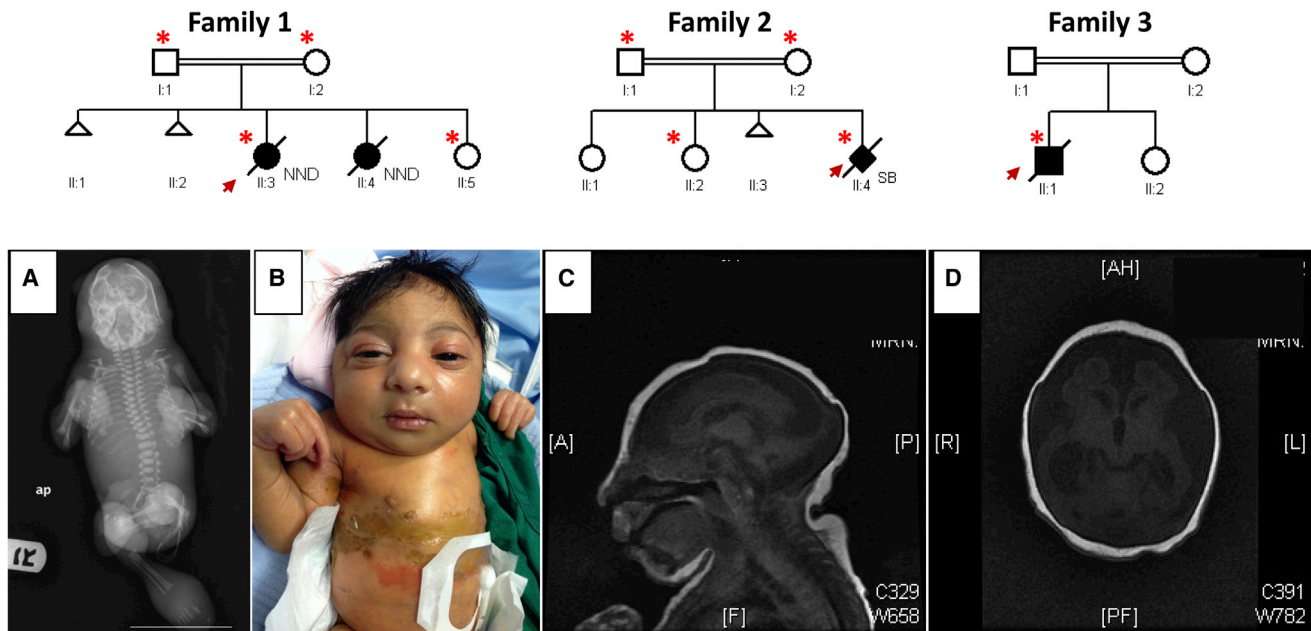
represent a sequence that is initiated by the brain malformation labeled as cerebroarthrodigital (CAD) sequence.<sup>7</sup> Contractures, which are common in NLS and sometimes accompanied by pterygium formation, are associated with hypoplasia of the skeletal muscles. Syndactyly of the hands and feet often takes an unusual form of severe swelling and rudimentary digits that are sometimes undiscernible.<sup>8</sup> The skin is usually ichthyotic with marked hyperkeratosis and can resemble the colloid membrane appearance of other ichthyotic disorders.<sup>9</sup> The face is highly characteristic with proptotic eyes, ectropion, eclabion, and a severely hypoplastic nose. Most affected children die shortly after birth, although survival beyond 10 months has been reported and presumed to represent a milder phenotype.<sup>10</sup>

The nature of this extremely severe multiple-congenital-anomaly syndrome has been debated for decades. In addition to the CAD sequence theory above, another proposal is that NLS might represent an inborn error of fat metabolism.<sup>8</sup> The latter was prompted by the often reported finding of significant accumulation of fat and myxoedematous material in the dermis throughout the body; this accumulation gives the typical edematous appearance of affected fetuses, who are sometimes referred to as being “hydropic.”<sup>11</sup> In this study, we took advantage of the powerful tools of autozygosity mapping and whole-exome sequencing to show that NLS is in fact an inborn error of serine metabolism and that a mouse model recapitulating key neurological and other features

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**Figure 1. Pedigrees and Clinical Images of the Study Families**

The index individual is indicated in each pedigree by an arrow, and asterisks denote individuals whose DNA was available for analysis. Abbreviations are as follows: NND, neonatal death; and SB, stillbirth.

(A) A babygram imaging of the index individual from family 2 shows small distorted calvarial bones without gross vertebral or tubular bone deformity.

(B) A photograph of the index individual from family 3 shows microcephaly, generalized colloidon-like ichthyosis, a sloping forehead, a broad nose, large ears, a short neck, spastic long fingers, and fixed contractures of the extremities.

(C and D) Axial (C) and sagittal (D) MRI of the index individual from family 3 shows a markedly atrophic and small brain with significant ventriculomegaly but normal appearance of the brainstem.

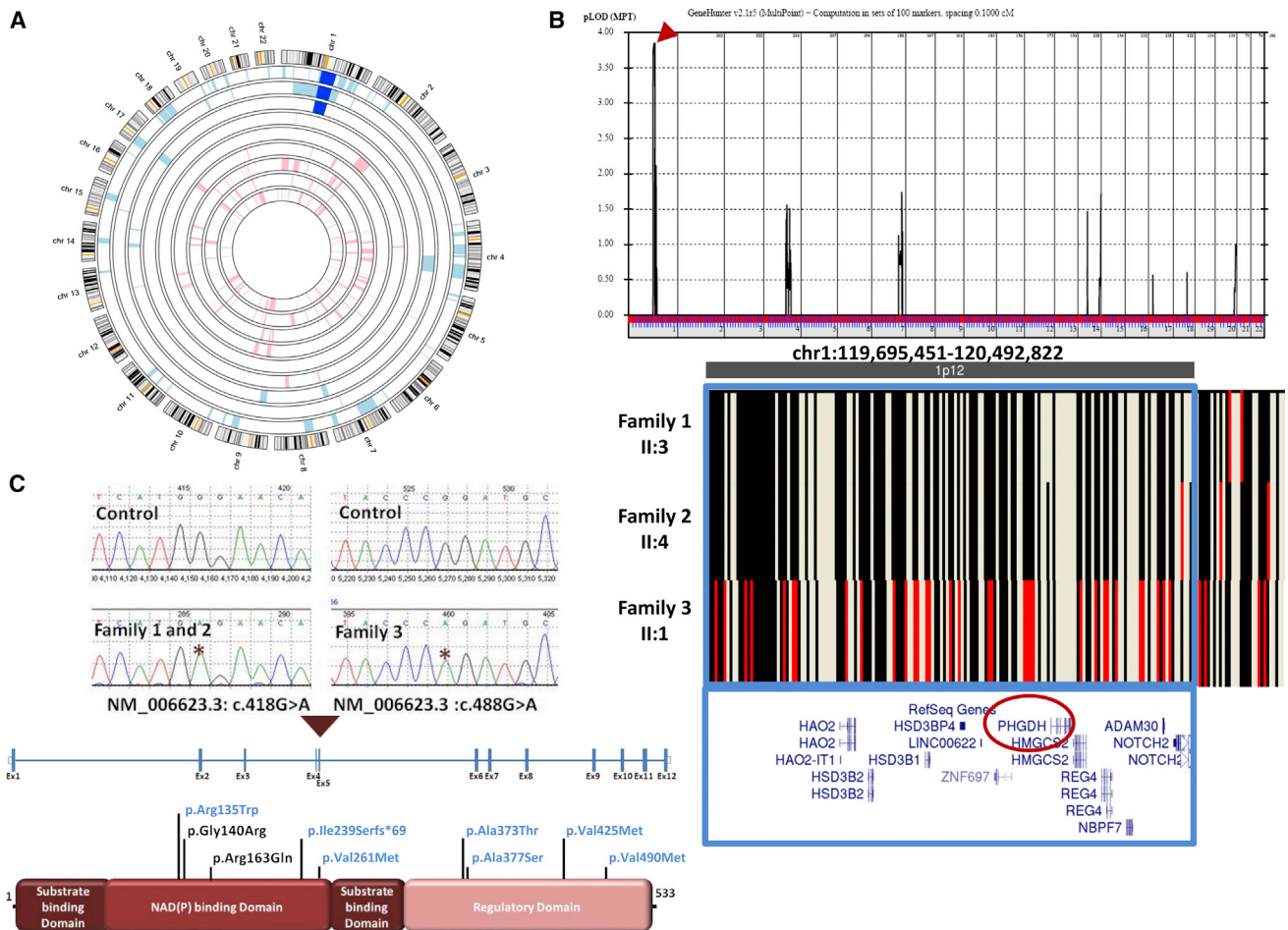
of this disorder can provide insight into its molecular pathogenesis.

Three affected individuals from three families were enrolled under a protocol approved by the institutional review board at King Faisal Specialist Hospital and Research Center (research approval committee 2080006) after signing written informed consent. Blood samples were collected from the affected individuals, their parents, and unaffected siblings when applicable. Family 1 consists of double-first-cousin Saudi parents with one healthy daughter, two spontaneous abortions, and one daughter who died immediately after birth and is said to have had the same phenotype as the index individual. This index individual (II:3 in family 1, Figure 1), a full-term female born vaginally, died immediately after birth. She was very small for her gestational age and had severe microcephaly (records of actual growth parameters at birth could not be retrieved), micrognathia, bulging eyes with absent eyelids, severe ichthyosis of the skin, cleft lip and palate on the right side, a very flat nose, a very short neck, and generalized edema. She also had extremely abnormal limbs with hypoplastic forearms and no discernible digits in the upper or lower limbs (Figure S1A, available online).

Family 2 consists of first-cousin parents and two healthy daughters. The index individual (II:4 in family 2, Figure 1) was born preterm at 29 weeks after an uneventful vaginal delivery. Antenatal ultrasounds at both 19 and 24 weeks of gestation showed polyhydramnios, curved vertebrae,

protruded eyes, an open mouth, low-set ears, a short and broad neck, microcephaly, generalized skin edema (especially of the trunk and scalp), abnormally flexed hands, extended crossed feet with a rocker-bottom appearance, and fetal akinesia. Postnatal screening for congenital infection was inconclusive. Postnatal examination revealed massive body swelling and marked disfigurement of the face and limbs, which appeared engulfed by a thin and shiny membrane (Figure S1B). The eyes were small, fixed, and widely spaced and showed supraorbital massive cystic swelling bilaterally. The nose was completely flat and obliterated, and the mouth was large and fixed open with massively swollen lips. The neck was extremely short. The ear lobules were edematous with tight overlying skin. The trunk was short and shiny with visible veins. The baby exhibited a fixed-flexion appearance with generalized contractures. The massively edematous hands and feet had no discernible digits. A skeletal survey showed defaced and overlapping cranial bones with severe soft-tissue edema. Thoracic, vertebral, pelvic, and other tubular bones had no major skeletal defects (Figure 1).

Family 3 consists of first-cousin parents with one healthy daughter and one affected boy (index) who died at the age of 1 month. The index individual (II:1 in family 3, Figure 1) was delivered vaginally at term with thick meconium-stained liquor. Birth weight was 2.24 kg. The baby was evidently jaundiced with generalized colloidon-like ichthyosis. He was microcephalic (head circumference



**Figure 2. Identification of a NLS-Associated Locus on Chromosome 1**

(A) AgileMultiIdeogram showing the chromosome 1 ROH (dark blue) shared among the index individuals from each of the three families. (B) Combined genome-wide linkage analysis of the three families revealed a single maximal peak (LOD score = ~3.9) on chromosome 1, and AutoSNPa output shows the critical interval at chr1: 119,695,451–120,492,822 (boxed in blue) within the shared ROH. The identical haplotype between individual II:1 in family 1 and individual II:4 in family 2 is denoted by black lines, whereas the red lines in individual II:1 from family 3 denote divergence in haplotype. (C) Upper panel: sequence chromatogram of the two missense mutations (control tracing is shown for comparison, and the location of each mutation is denoted by an asterisk). Lower Panel: schematic of PHGDH and the locations of the two homozygous missense substitutions identified in the three families (previously reported substitutions in individuals with PHGDH deficiency are shown in blue for comparison).

of 27.5 cm) with a sloping forehead, a broad nose, large ears, a short neck, spastic long fingers, and fixed contractures of the extremities (Figure 1). He succumbed to pneumonia and pseudomonas sepsis and died at 1 month of age.

Autozygome analysis was performed on all affected individuals with the Axiom SNP platform (Affymetrix) and was followed by AutoSNPa genome-wide determination of runs of homozygosity (ROHs) as surrogates of autozygosity essentially as described before.<sup>12,13</sup> Autozygomes of the index from the three families overlapped on a single chromosome 1 locus corresponding to the genomic region chr1: 117,058,389–159,754,449 bp (hg19 assembly, UCSC Genome Browser; Figure 2 A). Linkage analysis revealed a single peak (LOD of ~3.9) corresponding to the same critical ROH highlighted by autozygome anal-

ysis (Figure 2B). Within the shared ROH, a region with an identical haplotype (chr1: 119,695,451–120,492,822, spanning 11 RefSeq genes) between the two index individuals in families 1 and 2 was identified, further narrowing the critical interval (Figure 2B). Exome sequencing of the index individual in family 1 revealed a missense variant (c.418G>A [p.Gly140Arg], RefSeq NM\_006623.3) in *PHGDH* as the only homozygous coding or splicing variant absent from public databases within that critical interval. Consistent with their shared haplotype, targeted Sanger sequencing uncovered the same variant in the index individual in family 2 (Figure 2C). We then fully sequenced *PHGDH* in the index individual (II:1) in family 3 and identified another homozygous missense mutation (c.488G>A [p.Arg163Gln], RefSeq NM\_006623.3) (Figure 2C). Both variants were absent in 450 Saudi exomes, the 1000



dysmorphology syndrome that was found to be an inborn error of pyrimidine metabolism.<sup>19</sup> Thus, our surprising finding that NLS is an inborn error of metabolism should be viewed in the context of a trend where whole-exome sequencing is demolishing arbitrary distinctions. In addition, we note that whole-exome sequencing has confirmed allelism between NLS and PHGDH deficiency, a surprising finding that could not have been predicted on clinical grounds.

PHGDH deficiency, an inborn error of serine metabolism, was first described by Jaeken et al. in 1996.<sup>20</sup> Although serine can be synthesized with alternative pathways, reports of PHGDH deficiency were viewed as evidence that PHGDH and the pathway in which it serves are the major source of this nonessential amino acid because affected individuals have low serine levels in plasma and CSF despite the intact nature of those alternative pathways. These individuals are almost uniformly microcephalic and delayed in their development, and epilepsy and intrauterine growth retardation are common features.<sup>21</sup>

Our finding that NLS and PHGDH deficiency are allelic disorders raises an obvious question: why do the phenotypes of these two disorders differ significantly? There are several possible explanations for this discrepancy. First, ascertainment bias makes it possible that only individuals at the mild end of the PHGDH spectrum present to metabolic specialists with the common referring diagnosis of nonspecific intellectual disability and epilepsy, whereas those with more severe deficiency present with structural anomalies and are referred instead to dysmorphologists, who are less likely to conduct a detailed metabolic assessment. We are not aware of any previously published NLS report that explicitly describes results of plasma amino acid measurements. Second, a closer look at the literature suggests that a spectrum does indeed exist such that it is conceivable to view NLS and PHGDH deficiency as part of a spectrum, as illustrated by the previously reported 10-month-old infant with a mild form of NLS. Third, it is possible that the mutations that cause NLS exert a more detrimental effect on the protein function than do those previously reported in PHGDH deficiency. For example, 3D modeling suggests that the previously reported p.Arg135Trp (c.403C>T) (RefSeq NM\_006623.3) substitution in PHGDH deficiency is likely to affect the protein more mildly than the adjacent p.Gly140Arg, which we report here (Figure 3). Fourth, mice that completely lack the murine ortholog of PHGDH display a universally lethal phenotype that recapitulates key pathogenic features of NLS.<sup>22</sup> The embryos do not usually survive beyond 13.5 days postcoitus, are extremely small in size, and have a limb phenotype (where the terminal limb bud is swollen and fails to digitize) that is remarkably similar to that of NLS. Moreover, the brains of these embryos are small and show evidence of abnormal development, as seen in NLS individuals.

Given the above features, *Phgdh*<sup>-/-</sup> mice make a valuable NLS disease model and provide insights into the molecular

pathogenesis of NLS. Serine is required for the synthesis of key brain lipids, including sphingolipids and gangliosides, and these are indeed markedly deficient in the brains of *Phgdh*<sup>-/-</sup> embryos.<sup>22</sup> These mice have also been shown to have reduced aminophospholipids (e.g., phosphatidylserine and phosphatidylethanolamine) in addition to a documented repression of protein translation initiation.<sup>23</sup> Interestingly, *PHGDH* is highly expressed in neuroprogenitor cells during embryogenesis and is expressed in glial cells of postnatal brains.<sup>24,25</sup> Indeed, complete deficiency of PHGDH is associated with a marked proliferation defect of neuroprogenitors of *Phgdh*<sup>-/-</sup> brains, which can explain the severe microlissencephaly, a phenotype that has been previously shown to result from a mitosis defect of neuroprogenitors.<sup>26</sup> On the other hand, heterozygous *Phgdh*<sup>+/-</sup> mice are completely normal, so it is conceivable that residual activity of PHGDH in previously published individuals with PHGDH deficiency (range 12%–25%) might have provided sufficient serine to overcome a particular threshold below which the major developmental defects of NLS take place. It is worth mentioning here that another serine-metabolism-related knockout mouse (*Psid*<sup>-/-</sup>) in which phosphatidylserine decarboxylase deficiency results in decreased synthesis of phosphatidylethanolamine is also characterized by embryonic lethality.<sup>27</sup>

Our direct observation of serine depletion in NLS and the encouraging results of serine supplementation to treat individuals with PHGDH deficiency raise interesting possibilities about the potential benefit of serine supplementation during pregnancy to treat NLS or at least mitigate the severity of its associated developmental defects.<sup>28</sup> The practicality of such an approach will most likely be limited by the inability to identify this very rare disorder sufficiently early in pregnancy, but it can theoretically be attempted in families with high recurrence risk, such as the families studied here.

In summary, we report on the identification of homozygous mutations in *PHGDH* and serine deficiency in individuals with NLS. This disorder thus seems to be an extremely severe expression of PHGDH deficiency. Our finding that NLS is an allelic disorder of the much milder PHGDH-deficiency phenotype highlights the additional layer of complexity in linking genes to human diseases in that although genes are limited in number, their pathogenic alleles are not, and each of these alleles can have its own phenotypic consequences. Genomic sequencing is a powerful tool in tackling this challenge.

### Supplemental Data

Supplemental Data include one figure and can be found with this article online at <http://dx.doi.org/10.1016/j.ajhg.2014.04.015>.

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## Web Resources

The URLs for data presented herein are as follows:

AgileMultiIdeogram, <http://dna.leeds.ac.uk/agile/AgileMultiIdeogram/>

NHLBI Exome Sequencing Project (ESP) Exome Variant Server, <http://evs.gs.washington.edu/EVS/>

Online Mendelian Inheritance in Man (OMIM), <http://www.omim.org/>

PolyPhen, [www.genetics.bwh.harvard.edu/pph2/](http://www.genetics.bwh.harvard.edu/pph2/)

RefSeq, <http://www.ncbi.nlm.nih.gov/RefSeq>

SIFT, [www.sift.jcvi.org/](http://www.sift.jcvi.org/)

UCSC Genome Browser, <http://genome.ucsc.edu>

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Supplemental Data

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Figure S1. (A) Postnatal photograph of the index from Family 2 showing severe microcephaly, micrognathia, bulging eyes with absent eyelids, severe ichthyosis of the skin, a huge cleft lip and palate on the right side, flat nose, short neck, and generalized edema. Also seen are hypoplastic forearms and no discernible digits in the upper/lower limbs. (B) Postnatal photograph of the index from Family 2 showing massive body swelling with marked disfigurement of the face and limbs that appeared engulfed by a thin and shiny membrane.