Published in final edited form as:

Ophthalmology. 2011 June ; 118(6): 1137–1144. doi:10.1016/j.ophtha.2010.10.009.

A Novel Mutation of *LAMB2* in a Multi-Generational Mennonite Family Reveals a New Phenotypic Variant of Pierson Syndrome

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Abstract

Purpose—To describe a novel laminin beta-2 (*LAMB2*) mutation associated with nephritic syndrome and severe retinal disease without microcoria in a large, multi-generational family with Pierson syndrome.

Design—Retrospective chart review and prospective family examination.

Participants—An extended consanguineous family of 52 members.

Methods—The eyes, urine, and serum DNA were evaluated in all family members after discovering 2 patients, both less than 10 years of age, with bilateral retinal detachments and concurrent renal dysfunction. Linkage analysis was performed in the 9 living affected individuals, 7 using the Illumina Human Hap370 Duo Bead Array and 2 using GeneChip 10K mapping arrays.

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No conflicting relationship exists for any author.

This data was presented in part at the Annual Meeting of the International Society for Genetic Eye Diseases and Retinoblastoma, Strasbourg, France, August 28–30, 2008, the American Society of Human Genetics, Honolulu, Hawaii, 2009 and the Annual Meeting of the American Society of Nephrology, San Diego, California, October 31, 2009.

This article contains online-only material. The following should appear online-only: Table 1, Figures 1, 2, 6.

Main Outcome Measures—The prevalence and severity of ocular and kidney involvement and genetic findings.

Results—Eleven affected family members were identified (9 living), all manifesting chronic kidney disease and bilateral chorioretinal pigmentary changes, with or without retinal detachments, but without microcoria or neurodevelopmental deficits, segregating in an autosomal recessive pattern. The causative gene was localized to a 9Mb region on chromosome 3. Comprehensive gene sequencing revealed a novel *LAMB2* variant (c. 440A>G; His147R) that was homozygous in the 9 living, affected family members, observed at a frequency of 2.1% in the Old Order Mennonite population, and absent in 91 non-Mennonite controls. The mutation is located in a highly conserved site in the N-terminal domain VI of *LAMB2*.

Conclusions—This study describes a novel mutation of *LAMB2* and further expands the spectrum of eye and renal manifestations associated with defects in the laminin beta-2 chain.

INTRODUCTION

Pierson syndrome (Online Mendelian Inheritance in Man 609049), first described in 1963,¹ is an autosomal recessive disorder first characterized as microcoria (small pupils) and congenital nephrotic syndrome that rapidly progresses to end stage renal disease (ESRD). Affected individuals have mutations in the laminin B2 gene (*LAMB2*), one of several extracellular glycoproteins expressed in the glomerular basement membrane,² ocular structures,^{3,4} and the neuromuscular synapse.^{5,6}

Although the initial reports of Pierson syndrome were primarily of infants with microcoria, neurologic defects, and fatal renal failure, recent descriptions include children with milder renal disease and varied ocular findings.^{7–10} Some investigators suggest that frame-shift or truncating mutations cause more severe phenotypes while missense mutations can lead to partially functioning laminins and milder disease.^{7–8} Microcoria of some form, however, has been a consistent finding of most cases.^{11–12} This study describes a novel *LAMB2* mutation associated with renal dysfunction and severe posterior ocular segment findings without microcoria, traced through ten Old Order Mennonite generations.

SUBJECTS and METHODS

This study was compliant with Health Insurance Portability and Accountability Act (HIPAA) regulations and Institutional Review Board approval was obtained. General medical and ophthalmic examinations, urinalysis, and genomic DNA analysis were performed on 52 members of an extended Old Order Mennonite family after discovering 2 family members, both less than 10 years of age, with bilateral retinal detachments and nephrotic syndrome.

Chart review, analysis of outside medical records, comprehensive ocular examinations, and renal function studies (creatinine, estimated glomerular filtration rate (eGFR), and isotopic glomerular filtration rate (iGFR) where indicated) were performed on all 52 family members. The 2 index cases were evaluated in the Department of Ophthalmology (JSP, BGM), Division of Nephrology (MCH, JMG) and the Department of Medical Genetics (NML) at Mayo Clinic, and all renal pathology specimens were analyzed and collated by MCH and SHN at the same institution.

Renal involvement was defined as nephrotic syndrome (urinary protein excretion > than 50mg/kg/day, serum albumin <3 g/dL ± hyperlipidemia and/ or edema) with either end organ involvement (as seen on diagnostic percutaneous biopsy) or end stage renal disease (ESRD) established by a history of dialysis or kidney transplant. Ocular abnormalities of

any form were recorded following complete ophthalmic examinations performed at Mayo Clinic and the Clinic for Special Children.

The gene was mapped in this family by analysis of 7 affected cases and 11 unaffected siblings using the Human Hap370 Duo Bead Array (Illumina, San Diego, CA) at the Mayo Genotyping Core facility. In addition to performing comparisons of the homozygous regions within the affected cases, a subset of single nucleotide polymorphisms (SNPs) spaced at approximately 250 kb intervals were selected in order to perform linkage analysis. After further removal of SNPs that were monomorphic in the genotyped subjects, the Rutgers map was used to convert the intermarker distances from kb to cM.¹³ For SNPs that were not on the Rutgers map, linear interpolation was used to calculate the genetic map distances from the flanking SNPs. Prior to analysis, we also removed SNPs that were closer together than 0.05 cM in order to reduce redundancy. The remaining 7,702 SNPs on the autosomes were used to perform a genome-wide linkage scan within this large family. To perform the scan, two large branches of the family were separated to remove several inbreeding loops and to obtain sub-pedigrees that were appropriately sized for Merlin.¹⁴ This linkage analysis package was used to perform parametric single point linkage analyses for all selected SNPs under a recessive disease model. Additionally, two distantly-related Mennonite children with ophthalmic findings from the Clinic for Special Children (Patients 1 and 2) were genotyped using GeneChip 10K Mapping Arrays (Affymetrix, Santa Clara, CA).

For mutation analysis, the 32 coding exons plus flanking exonic regions of *LAMB2* were amplified by PCR and directly sequenced. The patients' *LAMB2* sequences were compared to the human reference sequence at NCBI (<http://www.ncbi.nlm.nih.gov/>, accessed September 1, 2009). Sequence variants were identified and compared to dbSNP (<http://www.ncbi.nlm.nih.gov/SNP/>, accessed October 3, 2009). SIFT¹⁵ (<http://blocks.fhrc.org/sift/SIFT.html>, accessed October 3, 2009.), PolyPhen¹⁶ (<http://genetics.bwh.harvard.edu/pph/>, accessed October 3, 2009.), and MacVector molecular modeling programs were used to assess putative pathogenic changes.

RESULTS

First Proband

An 8-year old girl (Figure 1, Patient 6, [available at <http://aaojournal.org>]) presented to Mayo Clinic with a 6-year history of glomerulonephritis, hypertension, and a recent diagnosis of retinitis pigmentosa. She was the product of an uncomplicated pregnancy and delivery, born at 35 weeks gestation with a birth weight of 4 pounds, 13 ounces. At 30 months of age she presented elsewhere with hematuria, proteinuria, and malignant hypertension leading to acute heart failure. A kidney biopsy was interpreted as proliferative glomerulonephritis for which she was treated transiently with oral corticosteroids, followed by enalapril, and aggressive blood pressure control. Her kidney biopsy was subsequently re-examined and revealed mild mesangial hypercellularity; however, no lesions of focal segmental glomerulosclerosis were observed. Ultrastructurally, podocytes showed extensive foot process effacement and there were a few mesangial electron densities identified. On immunofluorescence, only trace mesangial staining for IgM was seen. At the age of 12, her renal function serum creatinine was 1.1 mg/dl, creatinine clearance 54 mL/min or 69 mL/min per 1.73 m², and 306 mg urine protein excretion per 24 hour on 40 mg of enalapril per day.

One year prior to our examination she was diagnosed with a cone-rod dystrophy on the basis of decreased a and b waves on electroretinogram (ERG) reading. Her ocular examination at our institution demonstrated a corrected vision of 20/250 bilaterally with normal ocular alignment and no evidence of nystagmus. The patient's anterior segments showed

significant lenticular spoking of both lenses, and her fundi demonstrated diffuse subretinal fibrosis of both eyes, with a complete retinal detachment of the left eye (Figure 2A and B, available at <http://aaojournal.org>).

A pars plana vitrectomy, membrane stripping, air-fluid exchange, endolaser with scleral buckling, and silicone oil placement was performed on the left eye. Eight weeks after surgery, the vision in the left eye was 3/350 and 5/225 in the right, the later due to a new retinal detachment. The right eye underwent a pars plana vitrectomy, membrane peel, scleral buckle, heavy liquid, air-fluid exchange, endolaser, and silicon oil injection. Two months after surgery, the vision had improved to 20/400 and the retina was flat on the buckle. At this time, vision in the left eye had dropped to hand motions (HM) and a redetachment of the inferior retina was observed, necessitating further vitreoretinal surgery and subsequent iridotomies for iris bombe and elevated intraocular pressure. The last vision reported, 3 years after her initial examination, was 20/150 in her right eye with an attached retina and silicone oil, and HM in her left eye.

Second Proband

A 43 month-old girl (Figure 1, Patient 3, [available at <http://aaojournal.org>]) was seen at Mayo Clinic for a retinal detachment of her right eye. Analysis of this case showed a similar phenotype to that of the first proband and prompted a detailed family analysis, which revealed that the 2 patients were related through a large, consanguineous Mennonite family.

Patient 3 had a history significant for visual impairment since a young age, and a recent evaluation for glasses had revealed the retinal detachment. The child was the product of an uncomplicated pregnancy and delivery, born at 40 weeks gestational age with a birth weight of 8 pounds, 2 ounces. Ocular examination demonstrated a visual acuity of light perception in the right eye and 20/160 in the left. Her external exam was normal and she had a right exotropia of 25 prism diopters. Anterior segments showed a dense nuclear cataract of the right eye but were otherwise normal. A B-scan of the right eye showed a funnel retinal detachment with large choroidals (Figure 3A). The left fundus demonstrated pigment mottling and clumping in the macula and posterior retina (Figure 3B). A demarcation line was noted in the temporal periphery with peripheral vitreoretinal adhesions and tractions. The choriocapillaris was diffusely atrophic. At 54 months of age she developed a complete, shallow retinal detachment of the left eye (Figure 3C). A proliferative vitreoretinopathy-like contracture of the posterior hyaloid was noted superotemporally, and a pars plana vitrectomy with scleral buckle and membrane peeling was performed. She subsequently developed a cataract of the left eye, for which she underwent surgery with intraocular lens (IOL) implantation. Her final postoperative vision, eight weeks after surgery, was 20/300.

A urinalysis at 43 months demonstrated a protein/osmolality ratio of 6.1 and 21–30 red blood cells per high power field. Predicted 24hr urine protein was 3.5g. Serum albumin was low at 3.4 g/dL while serum creatinine was normal at 0.4 mg/dl. A needle biopsy of the kidney showed mesangial hypercellularity with mesangial IgM deposition by immunofluorescence and segmental (30%) podocyte foot process effacement with segmental paramesangial electron dense deposits on electron microscopy (Figure 3D). The patient was treated with lisinopril 2.5 mg/day. At 7 years of age, her predicted 24 h protein decreased to 1.8 g, serum albumin increased to 4.1 g/dl and serum creatinine remained normal at 0.3 mg/dl on her anti-proteinuric therapy.

Identification and analysis of further affected cases

Further analysis of 52 family members from 3 generations included sample collections and physical examinations. Seven different branches of the family, including Mennonite

individuals identified through the Clinic for Special Children in Strasburg, PA, were included in the study. The mean age of subjects was 17.5 years (range, 4 months to 68 years) and 29 (55.8%) were female. The extended family pedigree included 11 affected members, 9 of whom were living (Figure 1, available at <http://aaojournal.org>). None of the affected family members had developmental delay or neurological deficits while the 43 unaffected family members were free of ocular, urinary, or general medical abnormalities, with the exception of adult-onset hypertension in one member.

The age at onset and the principal ophthalmic and renal findings of the 9 affected members are shown in Table 1 (available at <http://aaojournal.org>). Ocular findings predated or were concurrent with renal abnormalities in 5 of the 6 patients with a clear medical history. The ocular findings for the 9 affected members (Figure 4), ranging in age from 3 to 42 years, included pigmentary retinopathy (N=6), unilateral or bilateral retinal detachments (N=5), band keratopathy (N=3), cataracts (N=3), nystagmus (N=2), bilateral optic nerve hypoplasia (N=1), microphthalmia (N=1), macular hypoplasia (N=1), and optic atrophy (N=1). None of the 52 family members had microcoria.

All 9 had nephrotic range proteinuria of variable severity. Proteinuria of up to 1214 mg albumin/m²-day was present at an early age, and resulted in hypoalbuminemia (3.1 g/dL) and hypogammaglobulinemia (378 mg/dL) in one 10 month-old infant (Patient 1). Hypertension was an early sign of renal involvement seen in two affected children under 2 years of age (Patients 1 and 2) with mean arterial blood pressures of 108 to 113 mmHg.

Chronic kidney disease progressed at variable rates; three patients (Patients 7, 8, and 10) required renal transplantation before 20 years of age whereas one 37 year-old patient (Patient 4), managed for many years with a calcium-channel blocker and angiotensin-converting enzyme inhibitor, had a stable glomerular filtration rate of 53 mL/min/1.73m².

Two nephrectomy specimens (obtained at the time of renal transplant in Patients 7 and 8) were available for re-evaluation. They showed advanced global glomerulosclerosis and tubulointerstitial scarring. Non-sclerotic glomeruli revealed moderate to severe mesangial hypercellularity and many glomeruli showed lesions of focal segmental glomerulosclerosis (Figure 5A–C). A biopsy specimen of Patient 6 demonstrated mild mesangial hypercellularity, rare lesions of focal segmental glomerulosclerosis, and <10% global glomerulosclerosis and cortical scarring. Additional renal findings included multiple large interstitial collections of foam cells (Figure 5D, Patient 8) observed in biopsy and nephrectomy specimens, and several collections of dilated atrophic tubules seen in a nephrectomy specimen obtained from Patient 7 (Table 1, available at <http://aaojournal.org>).

Despite multiple branches of the same family being affected, the disease phenotype was not observed in the parents of affected children, and the multiple consanguineous loops were consistent with a recessive pattern of inheritance. Parametric linkage analysis of 7 affected cases showed a maximal LOD score (3.25) on the short arm of chromosome 3 (Figure 6A, available at <http://aaojournal.org>). The next strongest peak was on chromosome 7 with a logarithm of odds (LOD) score of 1.7. Analysis of haplotypes revealed an approximately 9Mb homozygous area in 3p21 (rs13353497; 46,573,381Mb – rs1994978; 55,708,430Mb). Of the large number of genes within this area, a potential candidate gene, *LAMB2* (49,133,551 – 49,145,603Mb), that encodes laminin beta 2 was highlighted. Sequencing of an affected case and an obligate affected parent identified just one likely pathogenic change, 440A→G, resulting in the substitution H147R that was homozygous in the patient and heterozygous in the parent (Figure 6B, available at <http://aaojournal.org>).

Subsequent to the mapping and mutation identification in the living, affected individuals of this extended Mennonite family, 2 additional Mennonite individuals with a related

phenotype (Patients 1 and 2) contacted the Clinic for Special Children in Strasburg, PA to undergo genetic screening. An ongoing mapping study of these 2 patients localized a putative gene for this phenotype to a 9.9 Mb region on chromosome 3. Comparison of the genotype data revealed that the gene localization overlapped with the Pierson syndrome pedigree and haplotype analysis revealed identical homozygous genotypes for 20 SNPs. Analysis of the entire family showed the H147R genotype in all nine affected cases; all obligate carriers were heterozygous and normal siblings either heterozygous or wildtype. An analysis of 91 non-Mennonite control subjects did not identify this mutation, while screening of 96 Old Order Mennonite control samples revealed two heterozygotes yielding a carrier frequency of 2.1%.

Histidine to arginine is a relatively conservative change of one basic amino acid for another; however, H147 is a highly conserved residue found in all *LAMB2* orthologs (Figure 6C, available at <http://aaajournal.org>). Furthermore, the site is conserved in the laminins *LAMB1* and *LAMB4*, although it is not conserved in the alpha or gamma forms. H147 is in the laminin – N region (Domain VI), and may interact with the glomerular basement membrane in the kidney. Two programs, PolyPhen and SIFT, were employed to more rigorously test the likely pathogenicity of this missense change. Both programs indicated a high likelihood of pathogenicity of this mutation. The analysis of secondary structure also suggested that H147R may disrupt an alpha-helical domain in the protein.

DISCUSSION

This study describes an extended family of 52 Mennonite individuals with a novel *LAMB2* mutation causing a variant of Pierson syndrome among 11 (9 living) affected members. The principal findings of the 9 survivors include infantile-onset nephrotic syndrome with mesangial proliferative glomerulonephritis and retinal dystrophy or detachment without microcoria, further demonstrating the wide variety of ophthalmic and renal findings associated with *LAMB2* mutations.

Pierson and coauthors first identified 2 siblings with a complex oculorenal disorder in 1963. Their report¹ and a recent study localizing the genetic defect to *LAMB2*,⁶ described patients with early onset chronic renal failure, severe neurodevelopmental deficits, and microcoria. However, variants of Pierson syndrome have recently been described, including patients with mild, isolated, or delayed-onset nephrosis,⁷ and cases with varied ocular abnormalities including retinal detachment^{8–10} and pupillary membrane remnants.⁹ Recent studies have suggested that patients with milder forms of Pierson syndrome have at least one missense or non-truncating deletion mutation, whereas patients with more severe disease have two truncating mutations.^{7,8}

LAMB2 is one of several genes associated with congenital nephrotic syndrome. In a recent investigation of patients from 80 families who developed nephrotic syndrome within the first year of life, two-thirds were caused by mutations in 1 of the following 4 genes: *NPHS1* (22.5%), *NPHS2* (37.5%), *WT1* (3.8%), and *LAMB2* (2.5%).¹⁷ Pierson syndrome is caused by mutations to the *LAMB2* gene⁶ which encodes the laminin beta-2 chain. Laminins are heterotrimeric extracellular glycoproteins consisting of alpha, beta, and gamma chains. They are major components of basement membranes, with important roles in cell adhesion, proliferation, differentiation, and migration.¹⁸ Laminin provides essential structural integrity to basement membranes, and deficiencies in this protein alter basement membrane structure. The beta-2 isoform of laminin is specifically expressed in the glomerular basement membrane, ocular structures, and the neuromuscular synapse.^{2–5} Laminin beta-2 deficient mice manifest short inner and outer segments of photoreceptors and have disrupted synaptic connections between photoreceptors and second order cells.¹⁹

Renal pathology in patients with Pierson syndrome has shown a spectrum of findings, from minor podocyte effacement to diffuse mesangial sclerosis, and peculiar crescent formation.²⁰ In contrast, in the Mennonite family reported here, the most prominent pathologic features were mesangial hypercellularity and segmental sclerosis, without significant mesangial sclerosis.

A recent report described the ophthalmic findings of Pierson syndrome in 17 patients from 16 different families.¹² Ocular findings predated or were concurrent with the renal findings in all but one patient whose nephrosis was diagnosed 4 weeks prior to his ophthalmic manifestation. Variation in corneal size was noted in all 17 cases, and microcoria occurred in 16 of the 17 patients, some with iris hypoplasia or abnormal architecture. Thirteen patients (76%) had cataracts and 4 (24%) were diagnosed with glaucoma. Persistent fetal vasculature was observed in 7 (41%) while a retinal detachment was reported in 4 (24%) of the 17 patients. Twelve (71%) of the 17 died from ESRD at a mean age of 8.3 years.¹²

Ocular abnormalities detailed in prior reports were concentrated in the anterior segment, principally microcoria, but also glaucoma and abnormalities of corneal diameter, iris, and lens. In contrast, none of the patients homozygous for *LAMB2* H147R had microcoria or other disorders of the anterior segment. While several of our patients did develop cataracts, they appeared to be secondary to long-standing retinal detachment. More importantly, the principal ocular findings of our patients were abnormalities of the posterior segment, including retinal thinning, pigmentary changes, nonrhegmatogenous retinal detachments, and secondary optic atrophy.

The mechanism of the phenotypic variability among patients with Pierson syndrome is unknown. Mutations at different regions of the gene may selectively or predominantly affect different portions of the eye, and ocular phenotype does not always appear to correlate with the severity of renal disease. Similarly, renal disease associated with the *LAMB2* H147R variant was highly variable, ranging from stable chronic nephrosis to juvenile-onset renal failure. It seems likely that environmental variables and the degree of residual function of the mutated protein influence the natural history of both kidney and ocular disease among Mennonite patients with Pierson syndrome.

This study reports the largest family with Pierson syndrome evaluated to date. Affected members presented with variable renal dysfunction and severe posterior segment findings without microcoria or neurodevelopmental deficits, further broadening the range of eye and kidney pathology associated with mutations in *LAMB2*. These findings suggest that children who present with unexplained renal insufficiency or nephrotic syndrome should undergo an ophthalmologic examination; similarly, unexplained retinal detachments in young children should prompt urinary protein excretion measurements. Although Pierson syndrome is rare, early identification of this disorder enables the initiation of renal protective medical management and alerts the clinician to potentially treatable ocular morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This study was supported by an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY, NIH grant DK58816, and funds from the Department of Ophthalmology and Division of Nephrology and Hypertension

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Figure 3.

Ocular and renal pathology manifested in the second proband (Patient 3). (A): A B-scan of the right eye demonstrates a funnel shaped retinal detachment with large choroidals. (B): Fundus photograph of the left eye at 43 months of age prior to retinal detachment. (C): Fundus photograph of the left eye at 54 months of age demonstrating a new retinal detachment. (D): Electron Microscopy of a renal specimen shows segmental podocyte foot process effacement (arrows). (X3400).

Figure 4.

Ocular manifestations of this novel variant of Pierson syndrome. (A): Fundus photograph of the right eye of Patient 4 at 37 years of age showing retinal thinning with a central break. (B): Fundus photograph of the left eye of Patient 4 at 37 years of age manifesting retinal thinning with optic atrophy. (C): Fundus photograph of the right eye of Patient 5 at 24 years of age demonstrating pigmentary retinopathy. (D): External photograph of the right eye of Patient 7 at 42 years of age showing a dense cataract and band keratopathy. (E): External photograph of the left eye of Patient 7 at 42 years of age manifesting phthisis. (F): Fundus photograph of the right eye of Patient 8 at 41 years of age demonstrates optic atrophy and retinal thinning with pigmentary changes. (G): External photograph of the left eye of Patient

10 at 31 years of age demonstrates a dense cataract and band keratopathy. (H): Fundus photograph of the right eye of Patient 10 at 31 years of age showing retinal thinning with pigmentary changes.

Figure 5.

Renal pathology associated with this novel variant of Pierson syndrome. (A): A glomerulus from Patient 7 demonstrating a lesion of focal segmental glomerulosclerosis with increase in matrix material, intramembranous hyalinosis, and adhesion to Bowman's capsule. The non-sclerotic portion of the tuft exhibits mild mesangial hypercellularity. (Periodic acid-schiff (PAS), $\times 200$). (B): A glomerulus from Patient 7 demonstrating marked global mesangial hypercellularity (PAS, $\times 200$). (C): Two glomeruli from Patient 8 exhibiting moderate global mesangial hypercellularity. The glomerulus on the right also shows a lesion of focal segmental glomerulosclerosis. (PAS, $\times 200$). (D): A specimen taken from Patient 8 depicting abundant interstitial foam cells, indicative of severe proteinuria. (H&E, $\times 100$).