Published in final edited form as:

Adv Exp Med Biol. 2019 ; 1185: 209–213. doi:10.1007/978-3-030-27378-1_34.

Natural History and Genotype-Phenotype Correlations in *RDH12*-Associated Retinal Degeneration

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Abstract

Mutations in retinol dehydrogenase 12 (*RDH12*) cause a severe early-onset retinal degeneration, for which there is no treatment. *RDH12* is involved in photoreceptor retinoid metabolism and is a potential target for gene therapy, which has been successful in treating *RPE65*-associated LCA. *RDH12*-associated retinal degeneration is particularly devastating due to early macular atrophy, which will likely impact therapeutic outcomes. Defining the unique features and natural history of disease associated with *RDH12* mutations is a critical first step in developing treatments. The purpose of this review is to aggregate and summarize the body of literature on phenotypes in *RDH12*-associated retinal degeneration to help map the natural history of disease and identify phenotypic milestones in disease progression. The results reveal a severe blinding disorder with onset in early childhood and frequent retention of reduced yet useful vision until adolescence. The severity is associated with genotype in some cases. Distinct phenotypic features include macular atrophy followed by bone spicule pigment early in life, in contrast to other forms of LCA which often have a relatively normal fundus appearance in childhood despite severe visual dysfunction. Formal natural history studies are needed to define milestones in disease progression and identify appropriate outcome measures for future therapy trials.

34.1 Introduction

Leber congenital amaurosis (LCA) is the earliest and most severe form of inherited retinal degeneration. Twenty-five responsible genes have been identified to date, including *RDH12*,which accounts for approximately 2-7% of LCA (Weleber et al. 1993; Thompson et al. 2005; Valverde et al. 2009; Mackay et al. 2011). Retinol dehydrogenases RDH12 and RDH8 act in photoreceptors as reductases to convert all-*trans*-retinal to all-*trans*-retinol. RDH8 acts in the outer segments of the photoreceptors, where this conversion is an essential step in the visual cycle. In contrast RDH12 performs this conversion in the inner segments of photoreceptors to reduce excess toxic all-*trans*-retinal that leaks into the inner segments in the presence of continuous illumination(Maeda et al. 2006; Maeda et al. 2007; Chen et al. 2012). In addition, there is evidence that RDH12 reduces lipid peroxidation products in the photoreceptors(Marchette et al. 2010; Chen et al. 2012). RDH12 thus plays a protective role

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and is unlike visual cycle genes in disease mechanism, which may have important clinical consequences. For example, early macular atrophy is a prominent feature of *RDH12*-associated LCA, while *RPE65*-associated LCA demonstrates better preservation of macular structure and vision loss out of proportion to structural loss, consistent with a functional defect in the visual cycle(Jacobson et al. 2007). This difference is critical when contemplating future gene-targeted therapies for *RDH12*-associated LCA and appropriate outcome measures.

This review summarizes published phenotypes associated with *RDH12* mutations and highlights genotype-phenotype relationships. The purpose is to further elucidate the specific features of *RDH12*-associated disease that may be distinct from other forms of LCA and to identify patterns of disease expression resulting from different genotypes. This lays the groundwork for identifying the best outcome measures and the best candidates for future gene therapy trials.

34.2 Methods

A literature search was performed in PubMed with terms “RDH12” or “Retinol dehydrogenase 12,” and publications were included with phenotypic data on human subjects with genetically confirmed *RDH12*-associated retinal degeneration. Eighteen publications were included and reported phenotypic data on 222 subjects(Janecke et al. 2004; Perrault et al. 2004; Thompson et al. 2005; Jacobson et al. 2007; Schuster et al. 2007; Sun et al. 2007; Benayoun et al. 2009; Valverde et al. 2009; Sodi et al. 2010; Walia et al. 2010; Mackay et al. 2011; Chacon-Camacho et al. 2013; Beryozkin et al. 2014; Kuniyoshi et al. 2014; Sanchez-Alcudia et al. 2014; Yucel-Yilmaz et al. 2014; Gong et al. 2015; Zou et al. 2018). Phenotypic data was published for 134 individual subjects, with the remaining 88 subjects included in aggregate data reporting. Quantitative data reported in this review are based on the 134 individual subjects. Not all publications included pedigrees, and therefore overlap in families between publications could not be determined. The papers were published from 2004 to 2018. The correlation coefficient between visual acuity and age was calculated using Microsoft Excel, and visual acuity was compared between genotypes using student t-test in Microsoft Excel.

34.3 Subjects and Phenotypes

The subjects ranged in age from 2 to 69 years at the time of evaluation, with an average age of 21, and median age of 20. Visual acuity (VA) was reported in 126 individuals, or 94%. LogMAR visual acuity ranged from 0.05 to no light perception (one eye). There was great variability in visual acuity, including a 45 year-old with 20/25 vision, and a 5 year-old with count fingers vision, whom notwithstanding, the next youngest subject with 20/200 or worse was 6. Fundus findings were reported in 80% of subjects. Macular atrophy was a prominent finding, documented in 78%, as young as 3 years of age. One subject (age 20) had Coats-like exudation in the macula. Posterior staphyloma was documented in 18% of subjects. Pigment migration was documented in 90%, as young as 4 years. The oldest subject without pigment was 26 years. Optic nerve pallor was documented in 23% of subjects with recorded

fundus findings, as young as 5 years. The oldest person with documented normal disks was 14 years.

Electroretinogram (ERG) results were reported for 79 individual subjects (59%). ERG rod and cone responses were universally reduced. The youngest subject with a non-recordable ERG was 3 years old, while the oldest subject with residual responses was 20 years. Visual field results were reported in 21% of subjects and were universally constricted.

34.4 Genotype-Phenotype Relationships

Given the high prevalence of early macular atrophy in *RDH12*-associated retinal degeneration, visual acuity may serve as a marker of progression early in disease. Figure 34.1 demonstrates the VA for all subjects by age, compared to the VA of subjects with the 7 most common homozygous genotypes: T49M, L99I, A126V, C201R, S203R, Y226C, and L274P (Table 34.1). The number of subjects for each genotype ranged from 3 to 12. For all subjects in the cohort, visual acuity was variable, but showed an age-associated decline (r=0.53) (Figure 34.1). The most common homozygous genotype was T49M, and these subjects had better visual acuity compared to the rest of the cohort (p=0.005), with a similar average age at evaluation. The majority of T49M subjects had visual acuity better than LogMAR of 1.0 (20/200) (Figure 34.1). The T49M mutation is known to decrease affinity for NADPH and lead to increased proteosomal degradation in cell culture, and T49M is expected to reduce reductase activity *in vivo*(Thompson et al. 2005; Lee et al. 2007; Lee et al. 2010). The T49M substitution is postulated to be a hypomorphic allele rather than a functional null, consistent with the overall milder phenotype and better visual acuity. Subjects with the L99I genotype also had better visual acuity, with no eyes worse than LogMAR of 0.2 (20/32), although this was a smaller group with only 3 subjects. Previous studies have shown that the L99I variant of RDH12 has reduced enzymatic activity at 10% of normal(Thompson et al. 2005), and the biologic basis for a more mild phenotype is unknown. All 3 subjects homozygous for L99I were in the Spanish population, and were noted to be early onset at age 1.5 to 3 years, but with relatively well preserved visual acuity even into adulthood, while the heterozygous state paired with a frameshift led to a severe phenotype with count fingers vision or worse in childhood(Valverde et al. 2009). In contrast, subjects with the other 5 homozygous genotypes have worse vision than the T49M or L99I subjects (mean LogMAR 2.1 vs 0.8), and worse vision than the rest of the cohort (mean LogMAR 1.5), although this is confounded by differences in age between groups. C201R has shown both decreased expression levels and severely reduced retinoid reductase activity at 5-10% of normal in transfected cells(Janecke et al. 2004; Sun et al. 2007). The Y226C RDH12 variant has been shown to have severely reduced enzymatic activity(Janecke et al. 2004), while the activity of the S203R variant has not been reported. The L274P variant has 5% normal reductase activity(Thompson et al. 2005).

34.5 Conclusions

Overall, these data point to a rapidly progressive degenerative process that starts in early childhood, before the age of 5, and generally progresses throughout childhood and adolescence to severe vision loss by the age of 20 years. Previous investigators have

highlighted the unique features of *RDH12*-associated retinal degeneration compared to other forms of LCA, including the early appearance of macular atrophy and peripheral RPE atrophy in early childhood, followed by bone spicule pigment in late childhood or early adulthood(Perrault et al. 2004; Schuster et al. 2007; Sodi et al. 2010; Mackay et al. 2011; Chacon-Camacho et al. 2013; Zou et al. 2018). This is contrast to other forms of LCA that demonstrate normal fundus appearance despite marked retinal dysfunction. Furthermore, *RDH12* subjects often retain useful vision in childhood and have mild to no hyperopia and even occasional myopia, in contrast to other forms of LCA with frequent hyperopia(Perrault et al. 2004; Schuster et al. 2007; Sodi et al. 2010; Walia et al. 2010; Zou et al. 2018). Posterior staphyloma can develop in more advanced disease(Kuniyoshi et al. 2014; Zou et al. 2018). Variation in phenotype may be partly explained by the pathogenic variants in *RDH12*, as outlined in this review, but investigators also emphasize the importance of genetic modifiers, both in the *RDH12* gene itself, as well as visual cycle genes and other interacting proteins(Thompson et al. 2005; Valverde et al. 2009). Effective therapy aimed at slowing progression and preserving vision will require intervention in early childhood. A natural history study is needed to characterize the rate of progression and define periods of rapid change.

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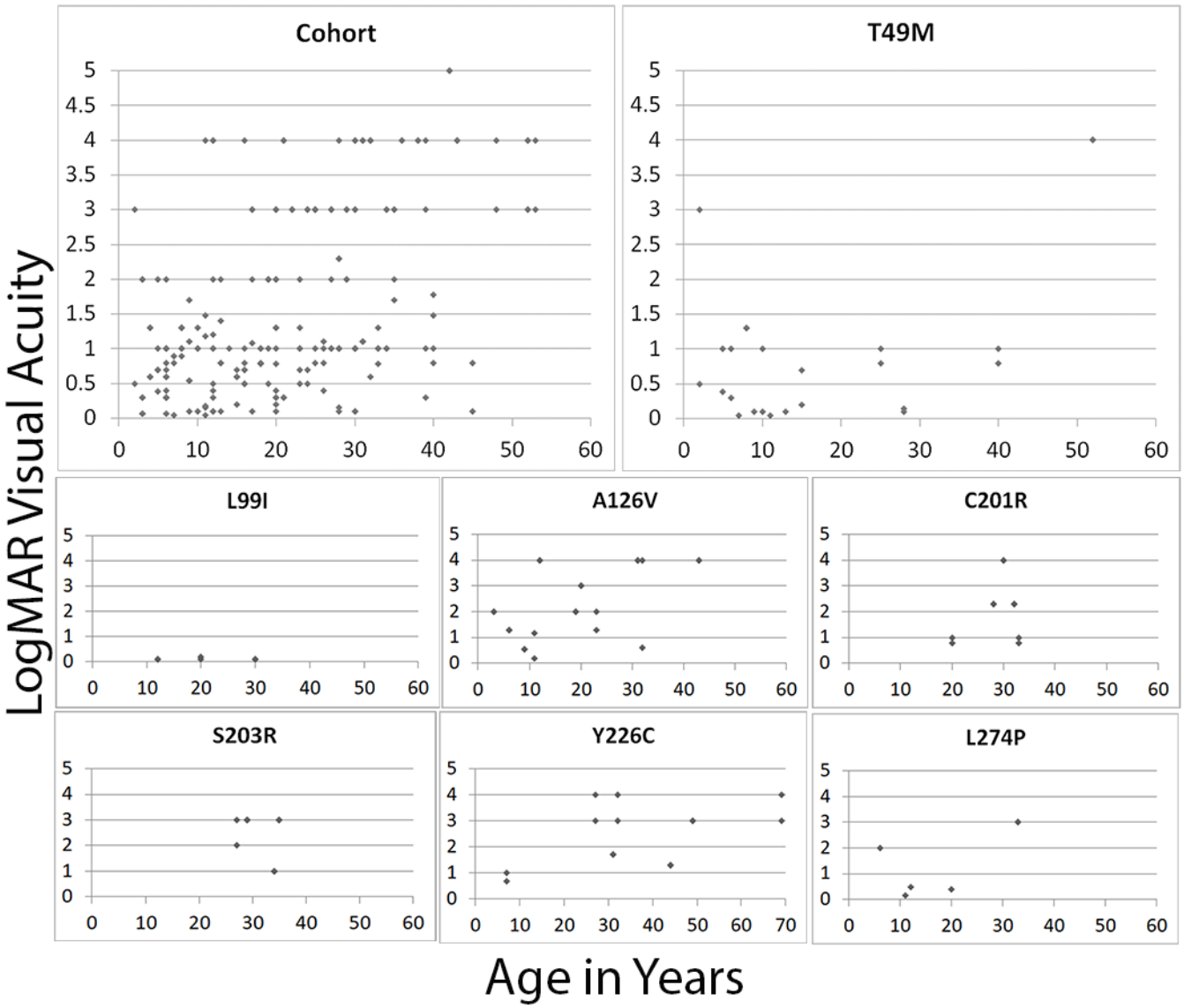

Fig. 34.1.

LogMAR visual acuity is shown in scatter plots by age for the entire cohort and for the 7 most common homozygous genotypes. For subjects with more than 1 encounter, the first visual acuity for each eye is plotted. Count finger vision was plotted as 2, hand motions as 3, light perception as 4, and no light perception as 5.

Table 34.1.
Most frequent homozygous genotypes in the literature and associated VA.

N=number of eyes. CF= count fingers. HM= hand motion. LP= light perception. Age range is shown in years (number of eyes in parantheses). VA range and median are shown in LogMAR (Snellen equivalent in parentheses). For subjects with multiple visits, only the first visual acuity for each eye is included.

Genotype (N)	Age Range (Mean)	VA Range	Est of VA Median
All Cohort (252)	2-69 (22)	0.05 (20/22) - NLP	1.0 (20/200)
T49M/T49M (24)	2-52 (18)	0.05 (20/22) - LP	0.75 (20/112)
L99I/L99I (6)	12-30 (21)	0.08 (20/24) - 0.2 (20/32)	0.1 (20/25)
A126V/A126V (22)	3-43 (19)	0.2 (20/32) - LP	CF
C201R/C201R (10)	20-33 (29)	0.78 (20/120) - LP	CF
S203R/S203R (8)	27-35 (31)	1.0 (20/200) - HM	HM
Y226C/Y226C (14)	7-69 (37)	0.7 (20/100) - LP	HM
L274P/L274P (10)	6-33 (19)	0.16 (20/29) - HM	1.25 (20/356)