March/April 2000 · Vol. 2 · No. 2

Outcomes analysis of verbal dyspraxia in classic galactosemia

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Purpose: This study evaluates a genotype/phenotype relationship between developmental verbal dyspraxia (DVD) and the common, missense mutation of the galactose-1-phosphate uridyltransferase gene, Q188R, in patients with classic galactosemia (G/G). **Methods:** As part of this study, we devised a questionnaire for "speech problems" to be completed by the patient's clinician. To validate the questionnaire and determine its accuracy in detecting DVD, we analyzed questionnaire responses for 21 patients by testing them independently and directly for DVD through a speech pathologist blinded to the patients' genotype. **Results:** We found that the questionnaire had a sensitivity of 0.56 and a specificity of 0.75. We then calculated the prevalence of DVD for a larger set of 113 patients with G/G galactosemia whose biochemical phenotype, molecular genotypes, and clinical status were known. The prevalence of "speech problems" from raw data were 50 of 113 (44.2%). After adjusting for misclassification, 43 (38.1%) were classified as cases of DVD. Using multivariate, logistic, regression analyses we found a significant interaction between genotype and mean red blood cell (RBC) galactose-1-phosphate (Gal-1-P). When corrected, using mean RBC Gal-1-P < 3.28 mg%, the Q188R/Q188R genotype was the best predictor of DVD. There was a significant risk (odds ratio = 9.6, $p = 0.0504$) of having DVD associated with homozygosity for Q188R compared with other genotypes. **Conclusions:** We conclude that homozygosity for Q188R mutations in the GALT gene is a significant risk factor for DVD. However, poor metabolic control obviates this relationship as indicated by RBC Gal-1-P greater than 3.28 mg%. ***Genetics in Medicine*, 2000:2(2):142–148.**

Key Words: *Galactosemia, verbal dyspraxia, genotype*

Galactosemia is an inborn error of metabolism caused by a deficiency of galactose-1-phosphate uridyltransferase (GALT) and resulting in the cellular accumulation of galactose, galactose-1-phosphate, and galactitol. Symptoms occur within the first weeks of life and include hepatotoxicity, cataracts, bleeding diatheses, sepsis, and death. Classic galactosemia (G/G) is an autosomal recessive disorder with an incidence between 1:30,000 and 1:60,000 livebirths in the United States.[1–3] Despite population-based, newborn screening and early dietary intervention, the clinical outcome of patients with G/G galactosemia is variable. Unexpected long-term dysfunctions include ovarian failure, growth and developmental delays, neurological signs of cortical and extrapyramidal tract impairment, and developmental verbal dyspraxia (DVD).[4–7]

Partially funded by grants from the National Institutes of Health including PO, 1, HD 2847 and MO1 RR0039.

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Received: November 15, 1999.

Accepted: February 3, 2000.

The GALT gene is located on chromosome 9p and is 4 kb in size with 11 exons and 10 introns.[8] More than 150 mutations in the GALT gene have been associated with GALT deficiency.[8] One common mutation in exon 6 of the GALT gene substitutes an arginine for a highly conserved glutamine at amino acid 188 (Q188R).[9,10] The Q188R allele is the most common mutation associated with the biochemical allele "G" of galactosemia among the Caucasian population with a prevalence of 70%.[8] This mutation ablates GALT activity by destabilizing the intermediate GALT-UMP and eliminating the second displacement reaction producing UDP-galactose.[11]

By defining G/G galactosemia through biochemical phenotype and molecular genotype, we, and others, attempted to clarify the mechanisms producing enigmatic outcomes. In one cross-sectional, retrospective study we found that homozygotes for Q188R had more "poor" outcomes than predicted by chance alone ($p = 0.019$).[10] Others did not find such an association.[12]

There have been no such attempts to relate the unusual speech disorder found in galactosemia to genotype or other environmental and epigenetic variables. DVD is the inability to produce volitional movements and sequences necessary for connected intelligible speech. Muscle pathology is excluded.[13] The term developmental indicates that the apraxia occurred before speech was acquired. Receptive language is normal, but

as expressive language is acquired, grammatical, vocabulary, and word deficits emerge. Previous studies have described the high frequency of general speech disorders among patients with galactosemia, and speech disorders were found in approximately 54% of patients.[4,12–15] In one report 56% of galactosemia patients had speech disorders, in response to questionnaires from multiple clinics.[4] While some studies have described the unique disorder of DVD among galactosemics, there have been no studies investigating the genotype of patients with G/G galactosemia and specifically defined DVD by formal outcome analysis. Early diagnosis of DVD is important because the disorder is recalcitrant to standard types of speech intervention and requires specialized speech therapy.[16]

The purpose of this study is to investigate the association of the GALT genotype and DVD among patients with classic galactosemia. To accomplish this goal we defined the validity of a questionnaire with regards to the general question of "speech problems" compared with DVD formally diagnosed by direct assessment in 21 patients with G/G galactosemia. We extended this formal outcome analysis of genotype on DVD by regression modeling in 113 additional patients with classic galactosemia whose GALT biochemical phenotype, molecular genotype, and clinical outcome questionnaires were contained in our database.

METHODS

Questionnaire

To investigate the genetic contribution of the Q188R mutation to the outcome of DVD, a large set of patients was necessary for a statistically meaningful study. For a study size of 21 patients with the observed frequency of homozygotes among those without DVD, the smallest detectable odds ratio is 9.2. While for a larger sample size of 113 patients the smallest detectable odds ratio is 1.0. Because it was logistically difficult to evaluate 113 patients from 31 centers by a speech pathologist for DVD, we devised a questionnaire that could be easily completed that included the question:

Speech disorders? Yes _ No _ Unknown _

We then coded "YES" as 1 and "NO" or "UNKNOWN" as 0. Combining the UNKNOWN and NO responses reduced the variability among different investigators' review. The creation of a dichotomous speech coding system reduced variables related to subjective judgment.

Validation of the questionnaire method

Because DVD is an unusual and specific subset of "speech disorders," we validated the questionnaire to determine the specificity and sensitivity of the responses to "speech disorders?" with respect to DVD. We received completed questionnaires for 36 G/G galactosemia patients over 3 years of age cared for in our clinic. Twenty-one of the 36 eligible patients signed informed consent forms and participated. The 15 patients who did not participate could not be located (N = 7), were too far away (N = 2), "had too many tests already" (N = 1), "doesn't need it" (N = 1), "too busy" (N = 3), or missed the appointed time for the evaluation (N = 1). An ANOVA analysis was performed to determine any significant differences between participants and nonparticipants for Age, Sex, Race, Genotype, Speech disorders, Highest Gal-1-P, and Mean red blood cell (RBC) Gal-1-P.[17] The 21 participants were then thoroughly examined by a speech pathologist, who was blinded to their GALT genotype. The examinations were done through a NIH sponsored General Clinical Research Center at Emory University. The Human Investigations Committee at Emory University approved this study. Following an initial hearing screen, the speech pathologist used *The Apraxia Profile* as an assessment tool to determine the presence or absence of apraxic characteristics.[18] The profile consists of six sections including an oral motor examination of verbal and nonverbal movements, word imitation, imitation of phrases and sentences, a connected speech sample, an apraxia checklist and a summary page of the results. A primary objective of an assessment for apraxia is the oral motor examination to determine if the child has competent abilities to coordinate each of the vocal tract structures (lips, tongue, mandible, velopharynx, and larynx) voluntarily and in a demand situation.

Since the *Apraxia Profile* was designed specifically to diagnose dyspraxic speech, we considered it the "gold standard." The questionnaires' information regarding speech, collected by subjective chart review for speech delays, was compared with the objective clinical evaluation for DVD. The sensitivity and specificity of the questionnaires' ability to detect DVD was then calculated. Where the sensitivity is the probability that the questionnaire response was "YES," given that the patient has DVD. Specificity is the probability that no speech delays were noted given that the patient does not have DVD.[19]

Outcome analysis for 113 patients with G/G galactosemia

These sensitivity and specificity measures were then applied to data collected from completed questionnaires for 113 patients with G/G galactosemia, from 31 different clinics. G/G galactosemia was defined as < 1% of control GALT activity in peripheral erythrocytes. Retrospective/cross-sectional information was collected, and signed informed consent was recorded for all 113 patients. Study eligibility required that the patient be over age 3, have biochemical phenotypes characterized, molecular genotypes recorded, and the question regarding speech delays completed on their corresponding questionnaire. Data were entered and analyzed by a Galactosemia Database that was designed and maintained at the Division of Medical Genetics at Emory University. Data included were: Date of Birth; Ethnicity; Age at initiation of dietary treatment; RBC galactose-1-phosphate; Urinary galactitol; GALT activity; GALT genotype. Datasets were exported into SAS for statistical analysis.[20] We transformed the raw data regarding speech delays, collected from the questionnaires, to the corrected data set regarding DVD, accounting for the sensitivity and specificity of the questionnaire method. An SAS program was written to randomly select subjects to correct for case misclassification. We did not perform separate analyses for the three genotypes Q188R/Q188R, Q188R/Other, and Other/Other, but assumed

the misclassification of DVD was the same regardless of GALT genotype. The Other allele was defined as any "other" GALT mutation, among the 113 patients with galactosemia that was not the Q188R allele. These data were then stratified by the three genotypes Q188R/Q188R, Q188R/Other, and Other/Other, and prevalences of DVD were calculated for each of the three genotypes. A Chi-square test of trend was performed to evaluate any significant differences between cases of DVD and controls for the variables of interest.[20]

Pearson correlations were evaluated among the covariates: Age, Sex, Race, Mean Gal-1-P, Highest Gal-1-P, and Genotype.[20] Significant correlations with genotype suggested effect modification of the genotype/phenotype relationship. That is, there may be a different effect of the genetic association with DVD depending upon the value of another variable. A multivariate logistic model was run to evaluate any effect modification suspected from significant correlations with the genotype.[21] The following two interaction variables were included in the model, (Mean Gal-1-P) × (Q188R/Other vs. Other/Other) as well as the product (Mean Gal-1-P) × (Q188R/Q188R vs. Q188R/Other). Two additional multivariate logistic regression models evaluated the association between the Q188R genotype and the outcome of DVD while controlling for possible confounding variables and the effect modification. This model was run only to ascertain possible interaction, not to report odds ratios. We modeled the probability of the dichotomous outcome of having DVD given the values of 6 independent variables: Highest Gal-1-P, Q188R/Q188R versus Q188R/Other, Q188R/Other versus Other/Other, Age, Sex, and Race.[21] The highest value of RBC galactose-1-phosphate (Gal-1-P) was analyzed as a variable. The highest Gal-1-P level was the amount of galactose-1-phosphate present in the red blood cell at the time of galactosemia diagnosis and before treatment was initiated. This variable assumed a measure of neonatal severity. Methods for determining red blood cell Gal-1-P were as previously described.[9,10,22] The highest RBC Gal-1-P was categorized into a dichotomous variable, either > 29.4 mg% or not. The genotype categories were determined by molecular genotyping as previously described.[9,10] Age was a continuous variable entered in years. Sex was a dichotomous variable, and race was categorized as Caucasian, Black, Hispanic, Ashkenazi Jewish, or Other/Unknown. This model was analyzed, stratifying by Mean Gal-1-P either < 3.28 mg% or not. The Mean Gal-1-P was calculated as the average of erythrocyte Gal-1-P concentrations measured at clinic visits, once a therapeutic level was achieved. The cutoff of 3.28 mg% was found by taking the average of all 60 calculated Mean Gal-1-P values. In the 60 calculations of the Mean Gal-1-P, three patients had Gal-1-P measurements taken after childhood. For 57 patients, the age range was from 10 days to 15 years. For only three patients were the Mean Gal-1-P calculated from measurements taken after age 15. For all patients the average number of measurements used to calculate the Mean Gal-1-P was 9. Therefore, the RBC Gal-1-P concentrations used to calculate a patients Mean Gal-1-P do span childhood and the Mean Gal-1-P variable is an environmental variable that includes dietary compliance and epigenetic factors. This variable was different from the Highest Gal-1-P and was called the Mean Gal-1-P. As part of the SAS analysis, a Hosmer-Lemeshow Goodness-of-Fit Statistic was calculated for each regression. The Hosmer-Lemeshow Goodness-of-Fit Statistic indicates how well the model describes the data. The p value for this statistic is the probability that any variation between the observed and the expected occurs by chance.[23]

RESULTS

Validation of the questionnaire method

The calculations of sensitivity and specificity from our questionnaire are described in Table 1. We analyzed difference in patient characteristics between the 21 participants and the 15 nonparticipants for DVD evaluations. Only sex was significant. More women participated probably due to parental concerns over ovarian failure as well as DVD. From the direct questionnaire responses, the prevalence of speech problems among the subset of 36 patients with G/G galactosemia was 0.38. By comparison the prevalence of DVD in the 21 participants who were directly assessed was 0.43. Eight out of 21 were stated to have speech problems while 9 of 21 were diagnosed with DVD. Three patients had speech problems that were not DVD, while four had DVD that was not described in the completed questionnaire. Thus there was a sensitivity and a specificity of 0.56 (0.35, 0.77) 95% and 0.75 (0.56, 0.94) 95%, respectively, to identify DVD (Table 1).

Outcome analysis for 113 patients with G/G galactosemia

The sensitivity and specificity measures of the questionnaire were then used to transform the raw data regarding "speech disorders" from completed questionnaires to an adjusted data set defining DVD in 113 patients with G/G galactosemia. For these patients the genotypes were distributed as Q188R/Q188R (N = 49, 43.4%), Q188R/Other (N = 42, 37.1%), and Other/Other (N = 22, 19.5%). A summary is tabulated of genotypes defined among all 113 patients with G/G galactosemia (Table 2). The average age was 13.6 years old and ranged from 3 to 41 years. Fifty-one patients were male and 62 were female. The ethnicity was distributed as Caucasian (N = 71), Black (N = 11), Hispanic (N = 1), Ashkenazi Jewish (N = 1), and Other/

Table 1
Validation of questionnaire with regard to Developmental Verbal Dyspraxia (DVD)

	Presence of DVD		
	YES	NO	
Questionnaire Response			
Yes	5	3	8[a]
No	4	9	13[b]
Total	9	12	21

[a]Sensitivity = 5/9 = 0.56; 95% C.I. (0.35, 0.77).
[b]Specificity = 9/12 = 0.75; 95% C.I. (0.56, 0.94).

Table 2
Observed genotypes among 113 patients with G/G galactosemia

Allele 1	Allele 2	Count
A320T	L195P	1
Deletion-5Kb	Deletion	1
Deletion-5Kb	Deletion-5Kb	1
IVSC	N314D-E203K	1
IVSF	Y209C	1
IVSF A–bp 1472G→A	K120N	1
K285N	K127E	1
K285N	P325L	1
L195P	unknown	1
M142K	L195P	1
Q188R	D113N	1
Q188R	DelC (bp2856)	1
Q188R	DELT (BP2959)	1
Q188R	E308K	1
Q188R	unknown	1
Q188R	H184Q	1
Q188R	K285N	7
Q188R	L195P	2
Q188R	L226P	2
Q188R	L289R	3
Q188R	Q188R	49
Q188R	Q344K	2
Q188R	R123Q	1
Q188R	R148Q	1
Q188R	S135L	4
Q188R	Unknown	8
Q188R	V151A	1
Q188R	Y209C	3
Q188R	Y251S	2
R148Q	R148Q	1
R201H	M336L	1
S135L	unknown	1
S135L	unknown	1
S135L	F171S	1
S135L	S135L	3
T138M	K285N	1
Unknown	Unknown	2
Y323D	Y323D	1
Sum		113

Unknown (N = 29). From the database 58% had values for "Highest Gal-1-P" and 53% for the "Mean Gal-1-P." The Highest Gal-1-P ranged from 10 to 184 mg%, with a mean of 29.4 mg%. The Mean Gal-1-P ranged from 1 to 10.24 mg%, with a mean of 3.28 mg%. Forty-seven percent of patients had "speech problems" according to the questionnaires. The prevalence of general speech problems among patients with the "Q188R/Q188R" genotype was 46.94%, among the "Q188R/Other" compound heterozygotes, it was 42.86%, and lastly, among the "Other/Other" homozygotes the prevalence was 40.91% (test of trend; $p = 0.608$).

After adjusting for misclassification, 43 of 113 (38.1%) patients were classified as cases of DVD. Nineteen patients (38.8%) with the "Q188R/Q188R" genotype had DVD. There were 16 (38.1%) compound heterozygotes with DVD. Finally, 8 (36.4%) Other/Other galactosemics had DVD. Therefore, four "Q188R/Q188R" patients classified as affected had to be reclassified as unaffected. Two of the "Q188R/Other" patients were reclassified as unaffected, and one of the "Other/Other" patients was reclassified as "unaffected." Table 3 compares the prevalence of "speech disorders" from the questionnaire with the derived prevalence of DVD by genotypes for all 113 patients. There was no significant difference for the prevalence of DVD among the three genotypes. (test of trend, $p = 0.853$). Of importance, however, is that this type of analysis does not control for possible confounding variables.

The results of logistic modeling performed to determine significant interactive variables are shown in Table 4. Mean Gal-1-P correlated with genotype as the only variable with significance. The first logistic model that included two interaction variables for the two genotype categories and Mean Gal-1-P revealed significant interaction between the genetic effect of homozygosity for Q188R and Mean Gal-1-P ($p = 0.033$) (Table 4).

Odds ratios were then calculated by logistic modeling to determine risk factors producing DVD while controlling for variables (Table 5). When Highest Gal-1-P, Age, Sex, and Race were controlled using logistic regression, there was a significant risk associated with the Q188R/Q188R genotype and

Table 3
Derived prevalence of Developmental Verbal Dyspraxia (DVD) by genotype in 113 patients with galactosemia

	Genotypes		
	Q188R/Q188R	Q188R/Other	Other/Other
Questionnaire Response*			
Yes	23 (47%)	18 (43%)	9 (41%)
No	26 (53%)	24 (57%)	13 (59%)
Total	49	42	22
DVD**			
Yes	19 (39%)	16 (38%)	8 (36%)
No	30 (61%)	26 (62%)	14 (64%)
Total	49	42	22

*Raw data from 113 questionnaires.
**Data derived from 113 questionnaires validated using a sensitivity of 0.56 and specificity of 0.75 for DVD (see Table 1).

Table 4
Logistic model to determine significant interactive variables with GALT genotype

Variable	Estimated Coefficient	Estimated Standard Error (SE)	Coefficient/SE	Chi-square *p* Values
Age	0.066	0.04995	1.75	0.1857
Sex	−0.767	0.6927	1.25	0.268
Q188R/Other	−0.46	0.9957	0.21	0.6439
Q188R/Q188R	2.187	1.1021	3.94	0.0472*
Race	−0.09	0.3871	0.054	0.8165
Highest Gal-1P	0.757	0.674	1.262	0.1896
Mean Gal-1-P	0.41	1.269	0.1046	0.7464
Q188R/Other × Mean Gal-1-P	0.574	1.5879	0.131	0.7176
Q188R/Q188R × Mean Gal-1-P	−2.292	1.3705	4.545	0.0330*

*Significant at alpha = 0.05.
−2 Log Likelihood = 72.926.
Goodness-of-fit Statistic = 6.2831 with 8 Degrees of Freedom (p = 0.6156).

DVD, depending on the patients' Mean Gal-1-P. The first model was run for only the patients with a Mean Gal-1-P > 3.28 mg% and there was no significant genetic risk for DVD. The Q188R homozygotes had an odds ratio of 0.327 of having DVD, when compared with the patients with the Q188R/Other genotype (p = 0.2412). While for patients with one copy of the Q188R mutation, the OR = 1.236, compared with the Other/Other patients, which was likewise not significant (p = 0.8704). This model has a Hosmer-Lemeshow Goodness-of-Fit Statistic equal to 9.8, p = 0.279; thus, this model describes only 27.9% of the variance in the data. Conversely, the next model was run for those patients whose Mean Gal-1-P was less than or equal to 3.28 mg% and were thus considered to have controlled dietary "compliance." For these "compliant" patients genotype was a significant risk factor for DVD. In patients with a Mean Gal-1-P < 3.28 mg%, homozygotes for Q188R had an odds ratio (OR) of 9.6 of having DVD, when compared with the patients with the Q188R/Other genotype (p = 0.0504). An odds ratio OR of 9.6 indicated that the Q188R homozygotes were approximately 10 times more likely to have DVD than the patients who were compound heterozygotes for the Q188R allele and another G allele. While for patients with one copy of the Q188R allele, the OR = 0.821, compared with the Other/Other patients, which was not significant (p = 0.8486). This model has a Hosmer-Lemeshow Goodness-of-Fit Statistic of 5.4, p = 0.7105, therefore, this model predicts 71% of the variance observed in the data (Table 5). This is a much better fit of the data than the 27.9% for the model when the patients included have a Mean Gal-1-P. The extent to which Mean Gal-1-P obfuscates the genetic contribution to DVD can be seen in Figure 1.

DISCUSSION

Many diseases are caused by complex interactions of genetics and environment.[24] Thus, our investigation of the genetic role in the physiologic and pathologic processes of galactosemia included environmental interactions in its analysis. Speech is a multifactorial function in humans and a multivariate logistic regression analysis was used to identify and control the effects of environmental interactions expected to confound an association with genotype.

Table 5
Logistic model to determine the risk factor of GALT genotype on developmental verbal dyspraxia controlling for a "compliance" variable

Variable	Estimated Coefficient	Estimated Standard Error (SE)	Coefficient/SE	Chi-square *p* Values	Odds Ratios	95% CI
Age	0.003	0.0729	0.0021	0.9635	1.003	(0.870, 1.157)
Sex	−0.955	1.1627	0.6751	0.4113	0.385	(0.039, 3.757)
Q188R/Other	−0.197	1.0314	0.0365	0.8486	0.821	(0.109, 6.200)
*Q188R/Q188R	2.263	1.1567	3.8275	0.0504	9.611	(0.996, 92.758)
Race	0.0193	0.7229	0.0007	0.9787	1.020	(0.247, 4.205)
Highest Gal-1-P level	1.046	1.1074	0.8927	0.3447	2.847	(0.325, 24.949)

*Odds ratio was determined on 29 patients with Mean RBC Gal-1-P less than 3.28 mg%.
−2 Log Likelihood = 33.746.
Goodness-of-fit Statistic = 5.4326 with 8 Degrees of Freedom (p = 0.7105).

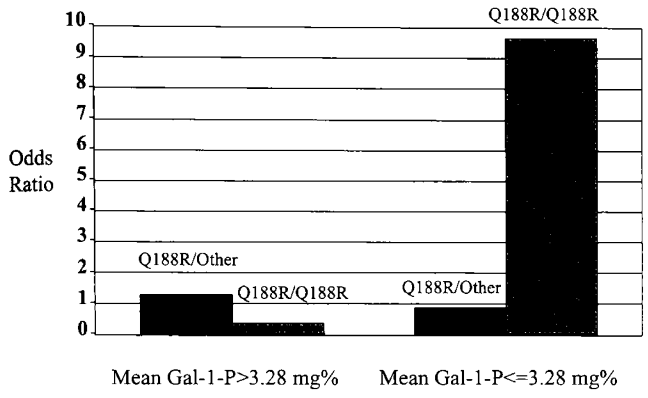

Fig. 1 Risk factor of genotype for dyspraxic speech revealed by high and low mean erythrocyte galactose-1-phosphate concentration.

The difference in risk of DVD between the Q188R homozygotes and the compound heterozygotes indicates the importance of this mutation. Homozygosity for Q188R ablates enzyme function by biochemical methods fully defined.[11] Thus a genotypic effect on outcome function was expected. However this effect was obviated by other variables that required definition. The variable, Mean Gal-1-P, reflected dietary compliance and other epigenetic factors such as galactose transport and galactokinase. Patients who, in theory, were less compliant with dietary galactose restriction might have increased risk for a poorer outcome associated with noncompliance, and other epigenetic factors, that outweighed the genetic contribution. This was observed and when controlled, the genotype Q188R/Q188R gave an odds ratio of nearly tenfold (Tables 4 and 5).

The second dietary variable, Highest Gal-1-P, did not significantly affect the model (Table 4). Similarly "the age at diagnosis" did not affect the logistic model (data not shown). These environmental variables were not interactive with genotype due to population-based newborn screening programs that identified babies born with galactosemia early in life. Most individuals of this patient population were diagnosed and treated within 14 days of life leaving little variation of the Gal-1-P accumulated in the erythrocytes among patients. Such a lack of variability minimizes the chances of observing a significant effect on the outcome of DVD. Yet, the long-term exposure to galactose that is reflected by the overall "dietary compliance variable," Mean Gal-1-P, does have greater variation among the patients. Therefore, when interaction with genotype was investigated, the significant role of dietary compliance in the development of DVD was found. We recognize the preponderance of Q188R/Q188R frequency could bias the results to inflate the association. To explore this bias we artificially created a data set where the genotype frequencies were equivalent. In this dataset we still see the association of Q188R homozygosity among those patients with Mean Gal-1-P <3.28 mg%, though not significant (OR = 6.7, $p = 0.11$), while we still see no association among those cases with Mean gal-1-P $>$ 3.28 mg%.

Of equal importance but less preponderance is the S135L G allele and its possible protective effect. There were three S135L/S135L homozygotes, four patients with the S135L/Q188R genotype, and three with the S135L/Other genotype. Among these patients there is a very low preponderance of DVD, only one of those with the S135L/Other genotype had noted speech delays. Furthermore, all 10 patients had a Mean Gal-1-P below 2.0 mg%.

Given these results, a child with galactosemia and possible DVD should benefit medically and mentally from an analysis of GALT genotype and dietary compliance followed by intervention where either parameter is a risk factor. The low sensitivity of physician recognition of DVD supports the view that GALT genotype must be considered when screening for DVD among patients with galactosemia. Apraxia can be diagnosed as early as 18 months with the review of the birth history, feeding history, motor development, and the child's ability to suck, chew, and swallow.[25] If DVD is present early, speech therapy should prevent predicted future educational problems. Typically, children from 2 to 5 years old expand their vocabulary from 200 words to 20,000 words.[16] If a child cannot acquire words in speech (as with a child having apraxia) they may not have the vocabulary to access, thus, causing word retrieval problems. Eventually the word retrieval problems lead to learning difficulties in the areas of reading, writing, and spelling.

An intervention plan for children with DVD differs from the traditional speech therapy and is most advantageous if initiated within the third year of life. Children with DVD do not make progress with traditional speech-language therapy for articulation and/or language disorders. They require frequent, more intense individual therapy sessions (2 to 3 sessions a week). The sessions focus on performing oral motor exercises, drills, and utilizing a multi-sensory approach incorporated into play activities. Important factors in determining if speech therapy will be successful is if the child is ready and able to attend to tasks in brief intervals and follow directions.

Thus far, only small sample sizes are available to study the risk factors for outcomes since galactosemia is a rare disease. However, the development of a Galactosemia database is a beginning for long-term, prospective studies investigating risk factors, the pathophysiological mechanisms found in patients with galactosemia, and interventions that can prevent expected poor outcomes. Genotyping the GALT gene in children with galactosemia will help in differentiating those patients who will benefit from early speech assessment and therapy to prevent learning disabilities.

Acknowledgments

We thank the following physicians for sending samples and clinical information on their patients: Dr. Anne Hing (Washington University School of Medicine in St. Louis, MO), Dr. Wendy Smith (Duke University Medical Center in Durham, NC), Dr. Howard Wolfinger (san Diego Imperial Counties Developmental Services, Inc. in San Diego, CA), Dr. Nancy Leslie (Children's Hospital Medical Center in Cincinnati, OH), Dr. Joel Charrow (Children's Memorial Hospital in Chicago, IL), Dr. Seymour Packman (Division of Medical Genetics at the

University of California at San Francisco, CA), Dr. Claire Leonard (University of Utah Health Sciences Center in Salt Lake City, UT), and Dr. Joan Pellegrino (St. Peter's Medical Center in New Brunswick, NJ). We thank faculty and staff of the Emory Genetics Laboratory for biochemical and molecular analyses and especially Sharon Langley for sequencing the GALT gene to define G mutations.

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