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The 3q29 Microdeletion Syndrome: Report of Three New Unrelated Patients and In Silico “RNA Binding” Analysis of the 3q29 Region

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Abstract

The human 3q29 microdeletion syndrome is associated with mild facial dysmorphism, developmental delay and variable congenital malformations. We report three new unrelated patients with this syndrome. We also performed in silico RNA binding analysis in silico on the 3q29 critical region genes. Several genes within this genomic region including *DLG1* and *RNF168* are predicted to bind RNA. While recessive mutations in *RNF168* cause RIDDLE syndrome, an immune deficiency and radiosensitivity disorder, the potential impact of heterozygous deletion of *RNF168* on patients with the 3q29 deletion syndrome is still unknown.

Keywords

chromosome; 3q29; aCGH; in silico; RNA binding; deletion

INTRODUCTION

Following the advent of microarray based technology, several novel submicroscopic microdeletion and duplication syndromes had been identified, including the 3q29 deletion (del 3q29) syndrome. Using subtelomeric fluorescent in situ hybridization (FISH), de novo del 3q29 syndrome was first identified in one young child with moderate intellectual disability, minor facial dysmorphism, horse shoe kidney, and hypospadias by Rossi et al. [2001]. Willatt et al. [2005] provided clinical and molecular characterization of the del 3q29 syndrome in six unrelated patients. Subsequently, several additional patients had been described. The syndrome is characterized by mild-moderate developmental delay, speech delay, mild nonspecific facial dysmorphic features, and variable structural abnormalities [Koolen et al., 2004; Baynam et al., 2006; Krepischi-Santos et al., 2006; Ballif et al., 2008; Shao et al., 2008; Digilio et al., 2009; Li et al., 2009; Mihçi et al., 2009; Pollazzon et al., 2009; Tyshchenko et al., 2009; Clayton-Smith et al., 2010; Quintero-Rivera et al., 2010; Wang et al., 2010]. Autistic traits have been noticed in a few patients [Willatt et al., 2005; Ballif et al., 2008; Quintero-Rivera et al., 2010]. All patients shared a small “sporadic” 1.6 Mb microdeletion except in three affected individuals with a familial deletion [Digilio et al.,

2009; Li et al., 2009; Clayton-Smith et al., 2010]. In this report, we describe three new unrelated individuals with 3q29 heterozygous deletion which does not include the human micro-RNA (*hsa-miRNA*) 570 gene. We also used in silico RNA binding analysis to characterize the deleted genes.

CLINICAL DESCRIPTION

Patient 1

An 18.5-year-old Hispanic man (Fig. 1a,b) was the product of uncomplicated term gestation and delivery to a 25-year-old healthy mother. His growth measurements at birth were normal [weight 3,895 g (75th centile), length 52 cm (75th centile), head circumference 35.5 cm (25th centile)]. He had a right inguinal hernia and a heart murmur which was associated with a small uncomplicated secundum atrial septal defect. Severe expressive language and articulation delays were diagnosed at 31 months of age. He received speech therapy for several years which was helpful. Hearing and vision evaluations were normal. Because of recurrent otitis media, he had tympanostomy tubes. He was thought to have a submucous cleft palate but did not require surgical correction. More recently, he had an arteriovenous hemangioma resected from his left arm. Family history was unremarkable. Currently, his weight is 62.65 kg (25th centile), height 172 cm (25th centile). He has mild facial dysmorphism (narrow and long face with prominent chin), and a high palate with few indentations. He also has mild pectus excavatum. He is a shy and soft spoken adolescent. He had a high resolution karyotype and FISH studies for the 22q11 deletion which were interpreted as normal. Array comparative genomic hybridization (aCGH) analysis revealed a 1.66 Mb deletion at 3q29 (Fig. 1e). Using the same FISH probe set, his mother's chromosomes demonstrated a normal hybridization pattern. His father was not available for analysis.

Patient 2

An 8-year-old Caucasian girl (Fig. 1c) was born at 36 weeks gestation which was complicated by maternal type 1 diabetes mellitus, significant hypertension, severe preeclampsia and polyhydramnios. Amniocentesis was normal (46,XX). Apgar scores were 6 and 8 and a patent ductus arteriosus closed by the second day of life. Failure to thrive, gastroesophageal reflux, urinary voiding dysfunction, ADHD and speech delay were diagnosed throughout early childhood. Family history was significant for attention deficit disorder in her sister while her mother had type 1 diabetes mellitus, hypothyroidism and multiple intestinal polyps. Routine chemistry studies including serum calcium, phosphorus and parathormone and 25-hydroxy vitamin D levels were unremarkable. Her bone age was normal. The patient's weight was 21.2 kg (10th centile), height 118 cm (<5th centile), and head circumference 51 cm (25–50th centile). She had bilateral epicanthal folds, normal eye slanting and prominent central incisors. She also had an interrupted transverse left palmar crease. Blood aCGH also revealed a de novo 1.66 Mb deletion at 3q29.

Patient 3

A 1.13 Mb deletion at 3q29 (base position chr3:197085422–198217248) was found in a patient referred to CMDX (Irvine, CA) for clinical aCGH analysis. The child had developmental delay, a heart murmur in addition to a paternally inherited paracentric inversion of chromosome 21 (not shown) based on the data provided to the laboratory at the time of clinical testing. No formal clinical genetics evaluation was available for this patient. No other structural or numerical chromosomal abnormalities were reportedly seen on the routine karyotype.

MATERIALS AND METHODS

Chromosome and FISH Analysis

GTG-banded chromosomes and FISH analyses were performed on peripheral blood lymphocyte cultures using standard techniques. The BAC clones RP11-793A14 (chromosome 3p11.1) and RP11-652M22 (chromosome 3q29) were obtained from The Center for Applied Genomics (TCAG, Toronto, Canada) and were used for FISH based confirmation of array comparative genomic hybridization (aCGH) results in all three patients.

Array Comparative Genomic Hybridization

Diagnostic whole-genome array-based comparative genomic hybridization (array CGH) was performed using the CMDX Oligo HD Scan™ (Irvine, CA) designed to detect genome-wide copy number variations. The array contains 99,000+ probes (Agilent Technologies, Santa Clara, CA) covering coding and non-coding human genome sequences with content sourced from the UCSC hg18 human genome (NCBI build 36, March 2006) and an average probe spatial resolution of ~21 kb. DNA copy number in the patient sample is evaluated in relation to a reference diploid DNA sample, and targeted evaluation of copy number changes involving >6 probes is performed in all regions of the genome including pericentromeric, subtelomeric, and loci representative of microduplication/microdeletion syndromes. FISH and/or BAC array CGH analysis using probes targeted to the region delineated by oligonucleotide array CGH is used for confirmation. Non-diagnostic copy number changes are referenced to the Database of Genomic Variants [<http://projects.tcag.ca/variation>; Iafrate et al., 2004] and percentage of overlap with polymorphic regions is determined. Nexus Copy Number™ software (Biodiscovery, El Segundo, CA) was used for copy number analysis across the genome.

In Silico RNA Binding Analysis

The RNABindR [Terribilini et al., 2007] and Pprint [Kumar et al., 2008] methods for prediction of RNA-binding propensity in specific amino acids of structurally un-resolved proteins were used to predict the RNA binding ability of the genes included in the deleted interval in chromosome 3q29. The default support vector machine (SVM) threshold value of -0.2 was used with the Pprint method. Both of these models were constructed from a training set of crystallographically characterized protein-RNA complexes available from the Protein Databank, with RNA-interacting residues being defined according to spatial proximity to RNA fragments. Genes were classified as likely RNA-binders (at least 25 consensus amino acids), possible RNA-binders (between 10 and 24 consensus amino acids), likely RNA non-binders (1–9 consensus amino acids) and RNA non-binders (0 consensus amino acids).

RESULTS

Oligo-aCGH analysis in all three patients reported here showed three submicroscopic subtelomeric deletions in chromosome 3q29 as shown in the representative profile in panel 1e. The 1.66 Mb deletion [base position chr3:197174369–198842531] appeared to be similar in the first two patients. It was confirmed by FISH analysis in all three patients using the BAC clone RP11-652M22 (data not shown). The deletion was appreciated in Patient 1 on retrospective examination of his karyotype. The mother of Patient 1 and both parents of Patient 2 had normal FISH analysis using RP11-65M22. The father of Patient 1 was not available for testing. BAC-aCGH analysis in Patient 2 also showed deletion of the 3q29 region encompassing RP11-480A16→RP11-652M22 (data not shown).

In silico RNA binding analysis showed multiple genes with potential RNA binding. As shown in Table I, they are ranked by the number of consensus amino acids with RNF168 (74/571) predicted to have the strongest RNA binding ability.

DISCUSSION

Large cytogenetically visible terminal deletions of chromosome 3 (3q27-ter) had been previously reported [Alvarez et al., 1984; Sargent et al., 1985; Brueton et al., 1989; Jokiahio et al., 1989; Chitayat et al., 1996; Senzaki et al., 2003; Pollazzon et al., 2009; Wang et al., 2010] in nine patients four of whom died in early childhood. As a group, they had significant structural abnormalities including cleft lip and palate, cerebral atrophy, Dandy-Walker malformation, meningocele and cardiomyopathy. Failure to thrive and short stature were frequent findings as well. More recently, Rossi et al. [2001] and then Willatt et al. [2005] identified and characterized a much smaller distal deletion limited to the terminal 3q29 band. Our three unrelated patients also have a very small terminal deletion (1.13–1.66 Mb) involving 3q29 which was easily identified and characterized using oligo-aCGH and confirmed by BAC-aCGH or fluorescent in situ hybridization. The relatively mild phenotype we report in these patients is consistent with the initial observations of Willatt et al. [2005] and others. While these patients have mild facial dysmorphic features, these features are not specific or clinically diagnostic. In the recent review by Quintero-Rivera et al. [2010], mild/moderate developmental delay (96%), speech delay (65%), microcephaly (58%) were the most commonly reported findings in patients with this syndrome. Also, unlike children who were born with larger “3q27-ter” deletions, children with the 3q29 deletion syndrome seem to have milder and fewer structural malformations including cleft lip/palate (4%), congenital heart disease (12%) and renal anomalies (8%) [Quintero-Rivera et al., 2010]. Congenital heart defects were reported in a father–son pair who also had 3q29 deletion [Li et al., 2009]. The father had pulmonic stenosis and PDA, while his son had subvalvular aortic stenosis and PDA. Patient 1 in this series had a hemodynamically insignificant secundum ASD without known family history of congenital heart disease while Patient 2 had prematurity-related PDA. *C3orf43* (base position chr3:197718147–197726634, hg18) is a gene located within the critical region for this syndrome, and it encodes a hypothetical protein LOC255798 which is expressed in heart, connective tissue and skeletal muscle [G2SBC database]. Given the complex inheritance of congenital heart disease and the unknown genotype–phenotype correlation for the deleted region on chromosome 3q29, it is not possible to confirm a direct causal relationship. The report of congenital microphthalmia and cataract in the patient reported by Tyshchenko et al. [2009] expands the phenotypic spectrum the 3q29 microdeletion syndrome. It is interesting to note that the breakpoints reported by Li et al. [2009] and Tyshchenko et al. [2009] overlap with the breakpoints we report here in these three patients.

The deleted 3q29 region contains a relatively small number of genes. While there is no known strong genotype–phenotype correlation, haploinsufficiency of *PAK2* and *DLG1* (also known as *SAP97*, synapse-associated protein 97) was thought to be responsible for the developmental delays seen in these patients. These two genes represent the autosomal homologues of known X-linked mental retardation genes, *PAK3* (OMIM No. 300142) and *DLG3* (OMIM No. 300189). *DLG1* and *CASK* (calcium/calmodulin-dependent serine protein kinase) are members of the membrane-associated guanylate kinase (*MAGUK*) protein family which represent scaffolding proteins associated with intercellular junctions. *Dlg* is expressed in murine epithelial, mesenchymal, neuronal, endothelial, and hematopoietic cells during embryogenesis and is required in normal craniofacial development, possibly in a subset of neural crest cells or their derivatives [Caruana and Bernstein, 2001]. Mice homozygous for the *dlg* mutation [Caruana and Bernstein, 2001] as well as *CASK* 22 insertional mutants exhibit prenatal growth retardation and secondary cleft

palate [Lavery and Wilson, 1998]. Through its L27 domain mediated homo and heteromulti-merization with other proteins, *DLG1/SAP97* regulates synaptic delivery of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) in hippocampal neurons [Nakagawa et al., 2004]. RNAi knockdown of endogenous SAP97 reduced surface expression of both *GluR1* and *GluR2* and inhibited both AMPA and NMDA excitatory postsynaptic currents. *PAK2* and *PAK3* are members of group (1) p21-activated kinases which have diverse cellular functions. Loss of function of *PAK3* is responsible for X-linked non-syndromic mental retardation whereas gain of *PAK3* function is associated with cancer [Kreis et al., 2008].

MicroRNAs (*miRNAs*) are a large family of small “17–25 nucleotides long” noncoding RNAs that posttranscriptionally extensively regulate gene expression in animals, plants, and protozoa. They interact with proteins and mRNA (by base pairing with the 3' untranslated region) causing translational repression and mRNA decay [Fabian et al., 2010]. Small RNAs including miRNAs are involved in a wide range of physiologic functions, such as developmental transitions and neuronal patterning, apoptosis, fat metabolism, and regulation of hematopoietic lineage differentiation [Jin et al., 2004; Qurashi et al., 2007; Stefani and Slack, 2008; Kim et al., 2009]. Their dysregulation is likely linked to the pathogenesis of neurological disorders [Cao et al., 2006; Stefani and Slack, 2008; Chang et al., 2009; Qurashi and Jin, 2010]. The roles of specific miRNAs have been explored in several neurodevelopmental disorders such as fragile X syndrome, Rett syndrome, velocardiofacial/DiGeorge syndrome and Down syndrome. Altered miRNA transcription and biogenesis, dosage of miRNA genes associated with segmental duplications, SNPs in the target sites throughout the human genome as well as variations in the target mRNA sequences could modulate the activity of specific miRNAs and alter phenotype accordingly [Clop et al., 2006; Georges et al., 2006]. Two miRNAs (570 and 922, base positions chr3 195,424,272–195,428,368 and 197,399,367–197,403,447, respectively) are encoded within the 3q29 region. Each of these two miRNAs is known to have many predicted downstream targets [miRBase database]. While miRNA 922 was deleted in Patients 1 and 2 and deletion involving this gene is a known CNV, miRNA577 was not deleted in any of our three patients. Given the large size deletions in patients with cytogenetically detectable 3q27-ter reported in the literature, we suspect that both miRNAs 570 and 922 were deleted as well which may explain their more severe phenotype and clinical heterogeneity. *C3orf43*, a gene consistently deleted in this syndrome is expressed in the heart and interacts with several downstream microRNAs [G2SBC database]. Based on the recent evidence which implicated DGCR8 (a gene within 22q11.2) in microRNA biogenesis and silencing of embryonic stem cell self-renewal [Wang et al., 2007], and in altered brain miRNA biogenesis leading to phenotypic abnormalities [Stark et al., 2008], we hypothesized that one or more of the deleted genes within 3q29 region may be an RNA binding gene and may exert a similar effect. We examined this possibility using the RNABindR and Pprint methods. The number of consensus amino acids predicted by both methods provides a reasonable measure of a protein's realistic likelihood of binding RNA, since a successful binding event is contingent upon favorable RNA-interaction with a significant number of surface amino acids. Surprisingly, several potential RNA binding genes within 3q29 were identified including *DLG1* (Tables I and II).

The RING finger protein RNF168 is a new ubiquitin ligase that functions as a chromatin modifier, through ubiquitination of histones H2A and H2AX [Pinato et al., 2009]. Its function is critical for DNA double-strand breaks repair (DSB) where it co-localizes with γ H2AX and 53BP1 which then increases the local concentration of ubiquitinated proteins. Recessive mutations in *RNF168* cause RIDDLE syndrome, a recently discovered syndrome which is characterized by Radiosensitivity, ImmunoDeficiency, Dysmorphic features, and LEarning difficulties [Stewart et al., 2007; Stewart et al., 2009; Stewart, 2009]. The father of

this patient with RIDDLE syndrome had chronic B-cell leukemia, suggesting that *RNF168* may also act as a tumor suppressor gene. In patients with radiosensitivity disorders, the underlying DNA double strand break repair defects have considerable impact on V(D)J gene recombination, class switching and lymphocyte maturation, leading to increased infections and cancer risk [Nahas and Gatti, 2009]. So far, none of the patients with the 3q29 deletion syndrome who are haploinsufficient for the *RNF168* gene was reported to have immunodeficiency or malignancy. DNA analysis of the *RNF168* intact allele and cellular radiosensitivity studies will be necessary to identify recessive mutations in these patients.

In conclusion, the phenotype seen in patients with the 3q29 microdeletion syndrome is somewhat non-specific and the structural malformations are relatively mild. The study of more patients and long term follow up of such individuals will help better define this syndrome and potential future risk of immunodeficiency and malignancy. This region of the genome encodes several putative RNA binding proteins which are predicted to play very important role in gene regulation and expression. The roles of these predicted RNA binding proteins and their interaction partners in the pathogenesis of this syndrome should be validated through direct experimental studies.

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WEB RESOURCES

The Center for Applied Genomics (TCAG). <http://www.cag.icph.org/http://www.cag.icph.org/>

Database of Chromosome Genomic Variants. <http://projects.tcag.ca/variation><http://projects.tcag.ca/variation>

Genes-to-Systems Breast Cancer (G2SBC) Database. <http://www.itb.cnr.it/breastcancer/><http://www.itb.cnr.it/breastcancer/>

miRBase: the microRNA database. <http://www.mirbase.org/><http://www.mirbase.org/>



FIG. 1. Facial profiles of patients 1 (a,b) and 2 (c) with the 3q29 deletion syndrome show narrow and long face (a,b), micrognathia (a), broad nose (c), and small mouth (a,d). Panel (d) ideogram and a partial karyotype of chromosome 3 in patient 1 shows a small deletion of 3q29. Panel (e) representative log₂ ratio probe plot for patients 1, 2, and 3 showing the 3q29 deletion. Note the CNV which overlaps the hsa-mir-922 gene. [Color figure can be seen in the online version of this article, available at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)1552-4833](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833)]

TABLE I

RNA Binding Analysis of the Genes Within the 3q29 Deletion Region

	Protein (number of consensus AA/total number of AA)
Likely RNA-binders (>25 consensus AAs)	RNF168 (74/571); SENP5 (50/755); DLG1 (43/904); AX747828 (37/245); TNK2 (isoform 1) (34/1048); FBXO45 (31/286); NCBP2 (30/86); TNK2 (isoform 3) (26/1086); LOC152217 (25/99)
Possible RNA-binders (10–24 consensus AAs)	KIAA0226 (21/972); MFI2 (20/738); WDR53 (19/358); TNK2 (18/528); PCYT1A (14/367); AK124973 (10/101)
Likely RNA non-binders (1–9 consensus AAs)	UBXN7 (7/489); PAK2 (5/924); TFRC (2/760); BDH1 (2/343); C3orf43 (1/206); LRC33 (1/692)
RNA non-binders (0 consensus AAs)	ZDHC19 (0/309); OSTAlpha (0/340); TCTEXID2 (0/142); KIAA0794 (0/341); TM4SF19 (0/209); OCTM4 (0/299); FIGX_I1 (0/258); FIGX_I2 (0/276); DKFZp686G18222 (0/100); FIGZ (0/86)

Within each group, proteins are ranked based on the number of surface amino acids predicted to be available for RNA binding.

TABLE II

Examples of RNA Binding Prediction Analysis

RNF168: uc003fwq.1 (RNF168) length=571	
74 consensus residues / likely RNA binding	MALPKDAIPSLSECQCIGICMEILVEPVTLPCHNHTLCKPCFOSTVEKASLCCPCFRRRRVSSWTRYHTTRNSL VNVVELWTHQKHYPRECKLRASQEQESEEVADDDYQPVRLLSKPGELRRREYEEIEISKVAAERRASBEENKAS EYEQIRLLAEBEIEEKRQAERKRAMEEQKSDDEELARKLSIDINNFCEGSIASPLNSRKSADPVPKSEK KSKNKORNI ¹ GDQKYLTPKSQFGSASHSEA ² QEVRRKDSVSKIDSSDRKSPGTQDTEIEDMPTLSPQISLG VGEQADSSIESPMPWL ³ CACGAEWYHEGAVKTRPSNHGKELCVLSHERPKTRV ⁴ VPYSKETAVMPCGR ⁵ TESGC APTSVVTQINGNNTETENEESCLLSKEISKRKNQESSFEAVKDFCSAKRRKVSPESSPQBEETEINF ⁶ T QKLDLHL ⁷ FERHKQEE ⁸ DRLLALQ ⁹ KEVD ¹⁰ KEQV ¹¹ PNRQ ¹² K ¹³ SP ¹⁴ DEY ¹⁵ HL ¹⁶ RAT ¹⁷ SS ¹⁸ PP ¹⁹ D ²⁰ K ²¹ VL ²² NG ²³ R ²⁴ K ²⁵ NP ²⁶ K ²⁷ DK ²⁸ G NEK ²⁹ R ³⁰ Q ³¹ TH ³² HT ³³ PE ³⁴ RG ³⁵ SR ³⁶ DK ³⁷ NR ³⁸ Q ³⁹ SL ⁴⁰ K ⁴¹ MI ⁴² QL ⁴³ K ⁴⁴ QS ⁴⁵ VN ⁴⁶ RR ⁴⁷ K ⁴⁸ MP ⁴⁹ NS ⁵⁰ TR ⁵¹ DH ⁵² CV ⁵³ SK ⁵⁴ AH ⁵⁵ LQ ⁵⁶ FS ⁵⁷ IS ⁵⁸ Q ⁵⁹ KS ⁶⁰ V ⁶¹ FQ ⁶² MF ⁶³ Q ⁶⁴ R CTK
SEN5: uc003fwz.2 (SEN5) length=755	
50 consensus residues / likely RNA binding	MKKQRKILWRKGHILAFSEKWN ¹ TGFGGFKFY ² FHQHLCILKALGR ³ PVTW ⁴ NRQLRHFQGRKKALQIQKT ⁵ WI KDEPLCAKTKFN ⁶ ATQNV ⁷ STLSSK ⁸ VKRKDAK ⁹ HFSSKTLRLQA ¹⁰ AEKLLSSAKNSDHE ¹¹ YCREKNLLKAV ¹² TD EFSNSALGOANGHRPRTDPSPDPMKFN ¹³ GESQSPGES ¹⁴ TVV ¹⁵ TLN ¹⁶ NH ¹⁷ K ¹⁸ R ¹⁹ K ²⁰ GFCY ²¹ CCO ²² GPE ²³ HR ²⁴ NG ²⁵ G ²⁶ PLJ PK ²⁷ Q ²⁸ LN ²⁹ QHRRIK ³⁰ L ³¹ PL ³² MMY ³³ EK ³⁴ SMIR ³⁵ F ³⁶ YRIL ³⁷ RSQ ³⁸ H ³⁹ FR ⁴⁰ TK ⁴¹ SK ⁴² Y ⁴³ KL ⁴⁴ R ⁴⁵ KA ⁴⁶ Q ⁴⁷ RS ⁴⁸ W ⁴⁹ V ⁵⁰ Q ⁵¹ Y ⁵² TG ⁵³ DH ⁵⁴ Q ⁵⁵ ET ⁵⁶ RR ⁵⁷ ENG ⁵⁸ E GGSC ⁵⁹ PPSP ⁶⁰ EP ⁶¹ DK ⁶² PC ⁶³ SR ⁶⁴ HQP ⁶⁵ Y ⁶⁶ PPDM ⁶⁷ SSA ⁶⁸ V ⁶⁹ K ⁷⁰ TN ⁷¹ SH ⁷² VD ⁷³ CH ⁷⁴ T ⁷⁵ K ⁷⁶ GS ⁷⁷ FL ⁷⁸ GK ⁷⁹ LS ⁸⁰ L ⁸¹ DE ⁸² AF ⁸³ PD ⁸⁴ QQ ⁸⁵ GS ⁸⁶ AT ⁸⁷ NA WD ⁸⁸ QSS ⁸⁹ SP ⁹⁰ K ⁹¹ W ⁹² ECT ⁹³ ELI ⁹⁴ HD ⁹⁵ PL ⁹⁶ PH ⁹⁷ RS ⁹⁸ NT ⁹⁹ MF ¹⁰⁰ ISE ¹⁰¹ TER ¹⁰² EIM ¹⁰³ TL ¹⁰⁴ Q ¹⁰⁵ EN ¹⁰⁶ Q ¹⁰⁷ TS ¹⁰⁸ SV ¹⁰⁹ SD ¹¹⁰ DR ¹¹¹ V ¹¹² KL ¹¹³ SV ¹¹⁴ SG ¹¹⁵ AD ¹¹⁶ TS ¹¹⁷ V ¹¹⁸ SS ¹¹⁹ VD G ¹²⁰ PV ¹²¹ S ¹²² Q ¹²³ KA ¹²⁴ VQ ¹²⁵ N ¹²⁶ SY ¹²⁷ Q ¹²⁸ ME ¹²⁹ ED ¹³⁰ GS ¹³¹ LK ¹³² QSIL ¹³³ S ¹³⁴ ELL ¹³⁵ D ¹³⁶ HP ¹³⁷ YC ¹³⁸ K ¹³⁹ SL ¹⁴⁰ E ¹⁴¹ APL ¹⁴² V ¹⁴³ CS ¹⁴⁴ GL ¹⁴⁵ K ¹⁴⁶ LEN ¹⁴⁷ Q ¹⁴⁸ VGG ¹⁴⁹ G ¹⁵⁰ K ¹⁵¹ NS ¹⁵² Q ¹⁵³ KA ¹⁵⁴ SP ¹⁵⁵ V ¹⁵⁶ D ¹⁵⁷ E QL ¹⁵⁸ SV ¹⁵⁹ CL ¹⁶⁰ FL ¹⁶¹ DE ¹⁶² V ¹⁶³ M ¹⁶⁴ KK ¹⁶⁵ Y ¹⁶⁶ SL ¹⁶⁷ PL ¹⁶⁸ SE ¹⁶⁹ K ¹⁷⁰ LV ¹⁷¹ GR ¹⁷² LK ¹⁷³ DF ¹⁷⁴ N ¹⁷⁵ DF ¹⁷⁶ NS ¹⁷⁷ R ¹⁷⁸ K ¹⁷⁹ PF ¹⁸⁰ IN ¹⁸¹ RE ¹⁸² IT ¹⁸³ Y ¹⁸⁴ RA ¹⁸⁵ R ¹⁸⁶ H ¹⁸⁷ Q ¹⁸⁸ KN ¹⁸⁹ CF ¹⁹⁰ RI ¹⁹¹ F ¹⁹² Y ¹⁹³ NK ¹⁹⁴ H ¹⁹⁵ M L ¹⁹⁶ MD ¹⁹⁷ DL ¹⁹⁸ AT ¹⁹⁹ L ²⁰⁰ D ²⁰¹ Q ²⁰² N ²⁰³ WL ²⁰⁴ ND ²⁰⁵ Q ²⁰⁶ VIN ²⁰⁷ MY ²⁰⁸ GEL ²⁰⁹ MDA ²¹⁰ V ²¹¹ PD ²¹² KV ²¹³ HF ²¹⁴ NS ²¹⁵ FF ²¹⁶ HR ²¹⁷ QL ²¹⁸ V ²¹⁹ TK ²²⁰ GY ²²¹ NG ²²² V ²²³ K ²²⁴ R ²²⁵ W ²²⁶ TK ²²⁷ V ²²⁸ DL ²²⁹ FK ²³⁰ KS ²³¹ LL ²³² L PH ²³³ LV ²³⁴ HW ²³⁵ SL ²³⁶ IT ²³⁷ VL ²³⁸ SN ²³⁹ RI ²⁴⁰ S ²⁴¹ F ²⁴² Y ²⁴³ DS ²⁴⁴ Q ²⁴⁵ GH ²⁴⁶ FK ²⁴⁷ FC ²⁴⁸ VEN ²⁴⁹ IR ²⁵⁰ K ²⁵¹ Y ²⁵² LL ²⁵³ TE ²⁵⁴ ARE ²⁵⁵ KN ²⁵⁶ RP ²⁵⁷ EL ²⁵⁸ Q ²⁵⁹ GW ²⁶⁰ QT ²⁶¹ AV ²⁶² T ²⁶³ K ²⁶⁴ CP ²⁶⁵ QQ ²⁶⁶ KN ²⁶⁷ D SD ²⁶⁸ CG ²⁶⁹ V ²⁷⁰ FL ²⁷¹ Q ²⁷² Y ²⁷³ CK ²⁷⁴ CL ²⁷⁵ A ²⁷⁶ L ²⁷⁷ EQ ²⁷⁸ PF ²⁷⁹ Q ²⁸⁰ S ²⁸¹ Q ²⁸² ED ²⁸³ MP ²⁸⁴ RV ²⁸⁵ RR ²⁸⁶ K ²⁸⁷ Y ²⁸⁸ K ²⁸⁹ EL ²⁹⁰ CE ²⁹¹ CR ²⁹² LM ²⁹³ D
DLG1: uc003fxo.2 (DLG1) length=904	
43 consensus residues / likely RNA binding	MPVRRKQD ¹ Q ² R ³ A ⁴ L ⁵ H ⁶ L ⁷ LEE ⁸ Y ⁹ RS ¹⁰ KL ¹¹ SQ ¹² ED ¹³ R ¹⁴ QL ¹⁵ RS ¹⁶ SI ¹⁷ ERV ¹⁸ IF ¹⁹ Q ²⁰ SN ²¹ L ²² FO ²³ AL ²⁴ ID ²⁵ IQ ²⁶ E ²⁷ F ²⁸ Y ²⁹ EV ³⁰ TL ³¹ LD ³² NP ³³ K ³⁴ CID ³⁵ RS ³⁶ K P ³⁷ SE ³⁸ PI ³⁹ Q ⁴⁰ V ⁴¹ N ⁴² T ⁴³ WE ⁴⁴ ISS ⁴⁵ LP ⁴⁶ SS ⁴⁷ TV ⁴⁸ SET ⁴⁹ L ⁵⁰ P ⁵¹ SSL ⁵² SP ⁵³ VE ⁵⁴ K ⁵⁵ Y ⁵⁶ Q ⁵⁷ ED ⁵⁸ TP ⁵⁹ Q ⁶⁰ E ⁶¹ H ⁶² IS ⁶³ PQ ⁶⁴ T ⁶⁵ NE ⁶⁶ V ⁶⁷ IG ⁶⁸ PE ⁶⁹ L ⁷⁰ V ⁷¹ H ⁷² SE ⁷³ K ⁷⁴ N ⁷⁵ L SEI ⁷⁶ EN ⁷⁷ V ⁷⁸ H ⁷⁹ G ⁸⁰ F ⁸¹ V ⁸² SH ⁸³ SH ⁸⁴ SI ⁸⁵ PI ⁸⁶ K ⁸⁷ TE ⁸⁸ AV ⁸⁹ L ⁹⁰ PS ⁹¹ P ⁹² TV ⁹³ VP ⁹⁴ IP ⁹⁵ LP ⁹⁶ PA ⁹⁷ EN ⁹⁸ TV ⁹⁹ IL ¹⁰⁰ PT ¹⁰¹ IP ¹⁰² Q ¹⁰³ AN ¹⁰⁴ PP ¹⁰⁵ V ¹⁰⁶ L ¹⁰⁷ V ¹⁰⁸ NT ¹⁰⁹ DS ¹¹⁰ LE ¹¹¹ TP ¹¹² Y ¹¹³ V NG ¹¹⁴ TD ¹¹⁵ AD ¹¹⁶ YE ¹¹⁷ BE ¹¹⁸ IT ¹¹⁹ LE ¹²⁰ R ¹²¹ GN ¹²² SL ¹²³ G ¹²⁴ FS ¹²⁵ IA ¹²⁶ GG ¹²⁷ TD ¹²⁸ NP ¹²⁹ H ¹³⁰ IG ¹³¹ DS ¹³² S ¹³³ IF ¹³⁴ IT ¹³⁵ K ¹³⁶ IT ¹³⁷ GG ¹³⁸ AA ¹³⁹ AQ ¹⁴⁰ DR ¹⁴¹ LV ¹⁴² ND ¹⁴³ CIL ¹⁴⁴ RV ¹⁴⁵ NE ¹⁴⁶ VD ¹⁴⁷ RD ¹⁴⁸ V ¹⁴⁹ TH ¹⁵⁰ SK ¹⁵¹ A ¹⁵² VE ¹⁵³ AL ¹⁵⁴ KE ¹⁵⁵ AG ¹⁵⁶ SV ¹⁵⁷ RL ¹⁵⁸ Y ¹⁵⁹ V ¹⁶⁰ K ¹⁶¹ RP ¹⁶² V ¹⁶³ SE ¹⁶⁴ K ¹⁶⁵ ME ¹⁶⁶ IK ¹⁶⁷ L ¹⁶⁸ K ¹⁶⁹ G ¹⁷⁰ L ¹⁷¹ G ¹⁷² FS ¹⁷³ IA ¹⁷⁴ GG ¹⁷⁵ V ¹⁷⁶ GN ¹⁷⁷ Q ¹⁷⁸ H ¹⁷⁹ IP ¹⁸⁰ GD ¹⁸¹ NS ¹⁸² I ¹⁸³ Y ¹⁸⁴ VT ¹⁸⁵ K ¹⁸⁶ IE G ¹⁸⁷ GA ¹⁸⁸ A ¹⁸⁹ H ¹⁹⁰ K ¹⁹¹ D ¹⁹² G ¹⁹³ K ¹⁹⁴ L ¹⁹⁵ A ¹⁹⁶ V ¹⁹⁷ NN ¹⁹⁸ V ¹⁹⁹ CL ²⁰⁰ EE ²⁰¹ V ²⁰² THE ²⁰³ EA ²⁰⁴ VT ²⁰⁵ AL ²⁰⁶ KN ²⁰⁷ T ²⁰⁸ SD ²⁰⁹ F ²¹⁰ V ²¹¹ LV ²¹² K ²¹³ Y ²¹⁴ AK ²¹⁵ PT ²¹⁶ SM ²¹⁷ IND ²¹⁸ GY ²¹⁹ APP ²²⁰ DT ²²¹ NS ²²² SS ²²³ QP VD ²²⁴ N ²²⁵ H ²²⁶ SP ²²⁷ SS ²²⁸ FL ²²⁹ G ²³⁰ Q ²³¹ T ²³² SP ²³³ AR ²³⁴ YS ²³⁵ PV ²³⁶ SK ²³⁷ AV ²³⁸ L ²³⁹ GD ²⁴⁰ DE ²⁴¹ IT ²⁴² RE ²⁴³ PR ²⁴⁴ K ²⁴⁵ WL ²⁴⁶ HR ²⁴⁷ GS ²⁴⁸ T ²⁴⁹ GL ²⁵⁰ FN ²⁵¹ IV ²⁵² GG ²⁵³ ED ²⁵⁴ GE ²⁵⁵ GF ²⁵⁶ IF ²⁵⁷ IL ²⁵⁸ AG G ²⁵⁹ P ²⁶⁰ AD ²⁶¹ LS ²⁶² G ²⁶³ EL ²⁶⁴ R ²⁶⁵ K ²⁶⁶ GD ²⁶⁷ RI ²⁶⁸ SV ²⁶⁹ NS ²⁷⁰ VD ²⁷¹ LR ²⁷² AA ²⁷³ SH ²⁷⁴ EQ ²⁷⁵ AA ²⁷⁶ AAL ²⁷⁷ KN ²⁷⁸ AG ²⁷⁹ QA ²⁸⁰ V ²⁸¹ TV ²⁸² AA ²⁸³ OY ²⁸⁴ R ²⁸⁵ PE ²⁸⁶ EY ²⁸⁷ SR ²⁸⁸ FE ²⁸⁹ AK ²⁹⁰ I ²⁹¹ HD ²⁹² LR ²⁹³ EQ ²⁹⁴ MM ²⁹⁵ NS ISS ²⁹⁶ SG ²⁹⁷ SL ²⁹⁸ RT ²⁹⁹ S ³⁰⁰ Q ³⁰¹ K ³⁰² RS ³⁰³ LY ³⁰⁴ VR ³⁰⁵ AL ³⁰⁶ FD ³⁰⁷ Y ³⁰⁸ DK ³⁰⁹ T ³¹⁰ KS ³¹¹ GL ³¹² PS ³¹³ Q ³¹⁴ LN ³¹⁵ PK ³¹⁶ FG ³¹⁷ DL ³¹⁸ H ³¹⁹ VA ³²⁰ SD ³²¹ DE ³²² W ³²³ Q ³²⁴ AR ³²⁵ Q ³²⁶ V ³²⁷ TP ³²⁸ DP ³²⁹ GE ³³⁰ S ³³¹ DE ³³² V ³³³ G V ³³⁴ IP ³³⁵ SK ³³⁶ RR ³³⁷ VE ³³⁸ KE ³³⁹ AR ³⁴⁰ L ³⁴¹ TV ³⁴² K ³⁴³ FN ³⁴⁴ SK ³⁴⁵ TR ³⁴⁶ DK ³⁴⁷ GE ³⁴⁸ IP ³⁴⁹ DM ³⁵⁰ GS ³⁵¹ GL ³⁵² K ³⁵³ H ³⁵⁴ VT ³⁵⁵ SN ³⁵⁶ AS ³⁵⁷ SS ³⁵⁸ Y ³⁵⁹ RG ³⁶⁰ EE ³⁶¹ Y ³⁶² VL ³⁶³ SY ³⁶⁴ EP ³⁶⁵ V ³⁶⁶ NO ³⁶⁷ QE V ³⁶⁸ NY ³⁶⁹ TR ³⁷⁰ VP ³⁷¹ III ³⁷² GP ³⁷³ M ³⁷⁴ K ³⁷⁵ R ³⁷⁶ IND ³⁷⁷ DL ³⁷⁸ ISE ³⁷⁹ PP ³⁸⁰ K ³⁸¹ FG ³⁸² SC ³⁸³ VP ³⁸⁴ HT ³⁸⁵ TR ³⁸⁶ K ³⁸⁷ RD ³⁸⁸ Y ³⁸⁹ VD ³⁹⁰ GR ³⁹¹ DY ³⁹² HF ³⁹³ VT ³⁹⁴ SR ³⁹⁵ EQ ³⁹⁶ ME ³⁹⁷ K ³⁹⁸ D ³⁹⁹ IQ ⁴⁰⁰ EH ⁴⁰¹ K ⁴⁰² IF ⁴⁰³ EA G ⁴⁰⁴ Q ⁴⁰⁵ YN ⁴⁰⁶ N ⁴⁰⁷ HL ⁴⁰⁸ Y ⁴⁰⁹ G ⁴¹⁰ TS ⁴¹¹ V ⁴¹² RE ⁴¹³ V ⁴¹⁴ AE ⁴¹⁵ K ⁴¹⁶ G ⁴¹⁷ K ⁴¹⁸ HC ⁴¹⁹ ILD ⁴²⁰ V ⁴²¹ SG ⁴²² NA ⁴²³ IK ⁴²⁴ RL ⁴²⁵ Q ⁴²⁶ IA ⁴²⁷ QL ⁴²⁸ Y ⁴²⁹ PS ⁴³⁰ IF ⁴³¹ PK ⁴³² SM ⁴³³ EN ⁴³⁴ IME ⁴³⁵ M ⁴³⁶ INK ⁴³⁷ RL ⁴³⁸ TE ⁴³⁹ EQ ⁴⁴⁰ AR ⁴⁴¹ K T ⁴⁴² FER ⁴⁴³ AM ⁴⁴⁴ K ⁴⁴⁵ LE ⁴⁴⁶ Q ⁴⁴⁷ E ⁴⁴⁸ FT ⁴⁴⁹ EA ⁴⁵⁰ IV ⁴⁵¹ Q ⁴⁵² G ⁴⁵³ DT ⁴⁵⁴ LE ⁴⁵⁵ DI ⁴⁵⁶ YN ⁴⁵⁷ Q ⁴⁵⁸ V ⁴⁵⁹ K ⁴⁶⁰ Q ⁴⁶¹ IE ⁴⁶² EQ ⁴⁶³ SG ⁴⁶⁴ SY ⁴⁶⁵ V ⁴⁶⁶ PA ⁴⁶⁷ KE ⁴⁶⁸ KL
AX747828: uc003fwo.1 (AX747828) length=245	
37 consensus residues / likely RNA binding	

MGRWETPPWILPGLPYSAWGFPLILPSKQSLRSSSAPPASGGLSPVKCKGTAEPTGLAVKAGGPEPARAT
AMAPRGPERGRAGRPGONDLAGFERKKGGEEMHRTAGLHREGKMKKEFEFGGPGAAPYSSRPRVPPAG
ADGLGPPFGLGWRGVGGSPSTLLGDRERGYREKGGAVSELNPEPTPTSSPLPQEGGRQLWVKPEGGMPEGK
GKFGADPLPAPDPTLHLPVTASLTGNGGELLN

RNABindR predictions are highlighted in red, while underlined amino acids are predicted by Pprint.