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Chromosomal microarray mapping suggests a role for BSX and Neurogranin in neurocognitive and behavioral defects in the 11q terminal deletion disorder (Jacobsen syndrome)

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Abstract

We performed a prospective analysis on 14 11q- patients to determine the relationship between the degree of cognitive impairment and relative deletion size. Seventeen measures of cognitive function were assessed. All nine patients with a deletion of at least 12.1 Mb had severe global cognitive impairment, with full-scale IQ <50, whereas all five patients with smaller deletions, ≤11.8 Mb, demonstrated mild cognitive impairment, with a full-scale IQ of 63 or higher ($p <$ 0.001). Among these five patients, the two patients with the larger deletions (11.4, 11.8 Mb) had a selective impairment in freedom from distractability compared to the three patients with smaller deletions (≤9.1 Mb). We propose the presence of a proximal critical region that contains a gene for global cognitive function and a distal critical region that contains a gene essential for auditory attention, which may be necessary for optimizing intellectual function. The proximal critical region is 300 kb and contains three annotated genes. One of these genes, BSX, encodes a brain-specific homeobox protein that in gene-targeted mice has been shown previously to have a role in regulating locomotory behavior via BSX-expressing neurons in the hypothalamus. The distal critical region, ~2.2 Mb, contains 18 annotated genes. One gene in this region, Neurogranin, has been demonstrated previously in mice to be critical for synapse plasticity and long-term potentiation. Taken together, our results implicate the presence of at least two loci in distal 11q that when deleted, cause global and selective deficits in neurocognitive function. These findings have important implications for genetic counseling and potential gene-specific therapies.

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Keywords

Jacobsen syndrome; Cognition; Comparative genomic hybridization; Brain; specific homeobox protein; Neurogranin

Introduction

The etiology of mental retardation, which occurs in about 4% of the population [1], is multifactorial and can be due to environmental and/or genetic factors. The severity of cognitive impairment or mental retardation (MR) is normally based on the evaluation of Full-Scale Intelligence Quotient (FSIQ), along with an assessment of adaptive abilities, in which MR is defined as an intelligence quotient of 70 or lower. Currently, more then 200 monogenic causes for MR can be found in OMIM.

Jacobsen syndrome (JBS, MIM 147791), also called the 11q terminal deletion disorder (11q-), is a contiguous gene disorder caused by the deletion of the end of the long arm of chromosome 11 [2]. The degree of mental retardation in patients with 11q- is variable [3]. Our previous studies included an initial genotype/phenotype analysis of cognitive function on 13 11q- patients [3]. Mapping of the deletion breakpoints by fluorescence in situ hybridization (FISH) demonstrated a strong correlation between deletion size and the degree of cognitive impairment. One of the limitations of this study was the inability to distinguish the breakpoints of patients that, by FISH, appeared to have similar size deletions. Recently, significant advances have been made that improve the resolution of deletion breakpoint mapping to the single gene level.

In this study, we set out to determine whether monogenic causes for the cognitive impairments observed in 11q- patients can be delineated. Accordingly, we performed a prospective genotype/phenotype analysis of cognitive function in 14 11q- patients. High-resolution copy number analysis using chromosomal microarray analysis (CMA) was performed on these patients in order to determine exactly which genes are deleted in individual patients. Our results implicate two loci in distal 11q whose deletion contributes to the cognitive impairments seen in 11q- patients. The more proximal critical region of ~300 kb contains three annotated genes, including BSX, which encodes a brain-specific homeobox protein [4]. The distal critical region is ~2.2 Mb and contains 18 annotated genes, including Neurogranin, a gene that is critical for synapse plasticity and long-term potentiation. We discuss the implications of these findings with respect to genetic counseling as well as for possible gene-specific therapies for patients with 11q-.

Materials and methods

Patient recruitment

Patients were recruited from the 11q Research and Resource Group conference held in June, 2006, in San Diego, California. Informed consent was obtained for all patients, in compliance with an Internal Review Board-approved protocol from the University of California, San Diego and San Diego State University.

Inclusion criteria

Inclusion criteria included any patient aged 6 years or older with a diagnosis of Jacobsen syndrome by a previous karyotype analysis. Only patients with pure distal 11q deletions were included. All patients were required to speak English as their first language.

Exclusion criteria

Patients with unbalanced translocations (i.e., deletion of distal 11q and duplication of another locus) were excluded. Patients were also excluded if they had a history of potential brain injury, such as severe prematurity (<32 weeks gestation), stroke, cardiac arrest/severe hypoxemia, and/or hypotension.

Cognitive assessments

An age-specific comprehensive analysis of intelligence was performed using the Wechsler Intelligence Test for Children III, WISC-III, or the Wechsler Adult Intelligence Scale-III (WAIS-III). Four broad categories tested included verbal intelligence, visual-spatial and synthetic intelligence, freedom from distractability/working memory, and full-scale IQ.

Deletion mapping

Deletion breakpoint mapping was performed using either the Affymetrix 500 K SNP platforms (average resolution ~10 kb) on eight patients and/or the Agilent 44B platforms (average resolution ~75 kb), also on eight patients (for two patients, both methods were used).

The Affymetrix Human Mapping 500K SNP array set consists of two arrays: the 250K Nsp array and the 250K Sty array. These assays were run by the UCCC microarray core facility following the protocol developed by the manufacturer. In short, 250 ng of genomic DNA is digested with 10 units of *Nsp*I or *Sty*I (New England Biolabs, Beverly, MA, USA) for 2 h at 37°C. Specific adaptors are then ligated onto the digested ends with T4 DNA Ligase for 2 h at 16°C. After dilution with water, samples are subjected to PCR using primers specific to the adaptor sequence with the following amplification parameters: 95°C for 3 min (initial denaturation), 95°C for 20 s, 59°C for 15 s, 72°C for 15 s for a total of 35 cycles, followed by 72°C for 7 min (final extension). PCR products are then purified and fragmented using 0.24 units of DNase I at 37°C for 30 min. The fragmented DNA is subsequently end-labeled with biotin using 100 units of terminal deoxynucleotidyl transferase at 37°C for 2 h. Labeled DNA is then hybridized onto the corresponding 250K Mapping Array at 48°C for 16–18 h at 60 rpm. The hybridized array is washed, stained, and scanned according to the manufacturer's instructions.

Interpretation of the copy number data was performed using Hidden Markov Models (HMM), as implemented in the software package CNAT4.0 (Affymetrix, Santa Clara, CA, USA). HMM analysis proposes that the experimental observation (the copy number signal of a given SNP locus) is the result of an unknown process, but that the underlying state (the "real" copy number of that locus) is relatively continuous. Parameters of this model include the number of states, the prior probability of each state, the transition probability between states, and the emission probability. In 11q-, these model parameters were tuned based on the assumption that the genome of these individuals was almost entirely diploid, with large regions (1–5 Mb) with altered CN. These constraints are reflected in the selection of five states (reflecting CN = 0, 1, 2, 3 and CN ≥ 4), with greatest prior probability assigned to CN = 2. The transition probability reflects the likelihood that the loci adjacent to one another will exist in the same state. Emission probability reflects the likelihood that an underlying state is emitted to produce the experimental observation. The HMM results were compiled and examined in genomic context (NCBI Build 36.1) using the UCSC genome browser.

Array-CGH mapping was performed using the Agilent Human Genome CGH Microarray Kit 44B (Agilent Technologies, Santa Clara, CA, USA). This platform is a high-resolution oligonucleotide-based microarray that allows genome-wide survey and molecular profiling of genomic aberrations with a resolution of about 75 kb. Labeling and hybridization were

performed following the protocols provided by Agilent. Briefly, 500 ng of purified DNA of a patient and of a control (Promega Corporation, Madison, WI, USA) were double-digested with *RSA*I and *Alu*I for 2 h at 37°C. After 20 min at 65°C, DNA of each digested sample was labeled by random priming (Invitrogen, Carlsbad, CA, USA) for 2 h using Cy5-dUTP for the patient DNA and Cy3-dUTP for the control DNA. Labeled products were column-purified and prepared according to the Agilent protocol. After probe denaturation and pre-annealing with 50 mg of Cot-1 DNA, hybridization was performed at 65°C with rotation for 40 h. After two washing steps, the arrays were analyzed with the Agilent scanner and the Feature Extraction software (v8.0). Graphical overview was obtained using the CGH analytics software (v3.1).

Statistical analysis

Data were entered, stored, and analyzed using the SPSS statistical software package (V15). Mean differences between the two deletion size groups were analyzed using Student's Independent Groups *t* test, adjusted for unequal variances when necessary. Spearman's rho coefficients were calculated to determine the degree of linear association between the ranking of the deletion size and several of the dependent measures.

Results

Fourteen patients were included in the study. Six of the patients (JS01, 03, 09, 12, 13, and 21) have been reported previously [3]. By karyotype analysis, 13 patients had a terminal 11q deletion, and one patient had an interstitial deletion at the end of 11q (11q23.3–11q25). There were seven males and seven females. Ages ranged from 6 to 25 years.

Table 1 lists the results of the cognitive testing for all 14 patients, in descending order of deletion size. In total, 17 parameters were determined. For some of the patients with the most severe deficits, not all of the parameters could be assessed. Figure 1 demonstrates the deletion breakpoints in distal 11q for all 14 patients, and the exact breakpoint intervals are listed in Supplemental Table 1.

Figure 2 demonstrates the correlation between full-scale IQ and deletion size ($p < 0.001$). FSIQ results led to a classification of two patient groups: Patients with the smallest deletions had mild cognitive impairment (64–81). These patients' deletion sizes ranged from 8.1 to 11.8 Mb. The eight patients with the largest size deletions and the one patient with interstitial deletion all had the most severe cognitive impairment, with overall scores below the level that could be meaningfully quantified (<50). The eight patients with terminal deletions from this group had deletion sizes that ranged from 12.1 to 14.3 Mb. One patient with severe cognitive impairment had an interstitial deletion that extended into the region deleted in the patients with the largest deletions, as well as partially into the region deleted in the five patients with mild cognitive impairment. All 17 parameters that were measured demonstrated a statistically significant difference when comparing the patients with deletion sizes of 11.8 Mb or smaller to those of 12.1 Mb or larger (Supplemental Table 2).

Among the five patients with mild cognitive impairment, we set out to determine if any of these patients had any significant differences in cognitive function between them. Although the numbers are small, there was a statistically significant difference for freedom from distractability (comprised of digit span and arithmetic) between the three patients with the smallest deletions (8.1–9.1 Mb) compared to the next two patients with slightly larger deletions but with overall mild neurcognitive impairment (11.4, 11.8 Mb) and the nine patients with severe neurocognitive impairment. None of the other parameters demonstrated a statistically significant difference between all three groups (data not shown).

Figure 3 displays the annotated genes located in the 300 kb minimal region that separates the smaller size deletion group (≤11.8 Mb) from the largest size deletion group (>/+12.1 Mb): BSX, ASAM, and HSPA8. In addition, there are 18 annotated genes within the 2.2 Mb distal region that distinguishes the patients with the three smallest deletions from the two patients with the next largest deletions that had a selective deficiency in freedom from distractability (data not shown).

Discussion

Our previous studies demonstrated a strong correlation between the degree of cognitive impairment and deletion size in patients with 11q-, implicating the presence of genes important for normal cognitive function in distal 11q. In the present study, we set out to perform a prospective analysis on 14 11q- patients to further refine critical regions for putative genes for cognition in distal 11q.

The patients with the largest deletions (at least 12.1 Mb), as well as the patient with the interstitial deletion, had severe cognitive impairment. The five patients with deletion sizes less than or equal to 11.8 Mb had relatively mild cognitive impairment. This suggests that there is a gene essential for global cognitive function located within a 300 kb region between the breakpoint of the patient from the group with mild impairment group with the largest deletion (11.8 Mb) and the patient from the group with severe impairment with the smallest deletion (12.1 Mb; Fig. 3). There are three annotated genes within this 300 kb region [4]: BSX, an evolutionarily highly conserved brain-specific homeobox gene; HSPA8, a member of the heat shock 70 kDa protein family; and ASAM, an adipocyte-specific adhesion molecule precursor. Interestingly, of these three genes, BSX is expressed early during brain development in the ventral diencephalon that will give rise to the hypothalamus and the primordium of the pineal gland [5]. BSX expression is maintained in these structures in the adult brain. Mice lacking BSX have been generated and shown to have altered locomotory behavior [6]. Although, to date, *Bsx* knockout mice have not undergone cognitive testing, the observed locomotory behavior defects in these mice demonstrate that BSX-expressing neurons in the hypothalamus can either directly or indirectly affect the function of higher brain structures, potentially those affecting cognitive functions. Based on the reported developmental expression pattern and previously known functions for *Bsx* in mice, we propose BSX as the most likely gene that underlies the severe global cognitive impairments observed in this subset of 11q- patients. Consequently, future studies aimed at defining the specific pathways involving BSX and cognitive function could potentially lead to the development of novel therapies. Although 11q- patients are only haplo-insufficient for BSX and heterozygous *Bsx* knockout mice have not been reported to have an obvious phenotype, this scenario is not unprecedented. For example, haplo-insufficiency for FOXL2 causes BPE syndrome in humans, whereas both copies of FOXl2 have to be deleted in mice to result in the same phenotype [7,8].

Among the five patients with mild cognitive impairment, there was a nearly statistically significant inverse relationship between deletion size and full-scale IQ. Moreover, there was a statistically significant inverse correlation between deletion size and one determinant of cognitive function, freedom from distractability/working memory index, which is comprised of digit span and arithmetic. Specifically, the three patients with the smallest deletions (8.1–9.1 Mb) had near-normal freedom from distractability/working memory index, whereas the patients with the next larger deletions (11.4, 11.8 Mb), with overall mild neurocognitive impairment, were selectively markedly impaired in freedom from distractibility/working memory index (data not shown). The nine other patients with severe neurocognitive impairment were also markedly impaired for freedom from distractilibility/working memory index. Although we only identified five patients with mild cognitive impairment, these data

suggest that there might be a gene important for freedom from distactability/working memory index within a ~2.2 Mb region from 9.1 to 11.4 Mb centromeric to the telomere. There are 18 known genes within this interval (data not shown). This putative gene(s) may be essential for preserving overall intellectual function and in particular, at least one specific aspect: auditory attention. Thus, auditory attention may be a prerequisite for optimizing intellectual function in these patients.

One gene that is within the distal 2.2 megabase critical region, Neurogranin, has been shown in mice to have a critical function in synapse plasticity and long-term potentiation [9–12]. Interestingly, hetero- and homozygous gene-targeted Neurogranin knockout mice demonstrate impairments in visual-spatial learning, sensitivity to stress, and anxiety. These observations may be analogous to the decreased freedom from distraction/working memory index function that we identified only in the 11q- patients that are haplo-insufficient for Neurogranin. Subsequent studies on Neurogranin knockout mice demonstrated that heterozygous knockout mice, when placed in an enriched environment (larger cages, frequent new toys, exposure to other mice, and unlimited access to an exercise wheel), had significant improvement in their learning and behavioral deficits. There was a concomitant increase in the Neurogranin protein level in the hippocampus to near-normal levels, as well as increased long-term potentiation. As predicted, homozygous knockout mice did not respond to environmental enrichment. Interestingly, wild-type mice (i.e., those with two copies of the neurogranin gene) also increased their neurogranin protein levels when exposed to an enriched environment [13]. Consequently, 11q- patients that are haplo-insufficient for Neurogranin may benefit from an enriched learning environment or any other intervention that can bolster Neurogranin protein levels in the hippocampus. Clearly, more patients with deletions less than 11.8 Mb will need to be studied to substantiate the role of Neurogranin in causing selective cognitive impairment in 11q- patients.

In summary, we have performed a comprehensive genotype/phenotype analysis on 14 patients with the 11q terminal deletion disorder. Patients with deletion sizes of ≥12.1 Mb have severe global cognitive impairment, while patients with deletion sizes ≤11.8 Mb have mild cognitive impairment. Furthermore, our data suggest that patients with deletion sizes ≤11.8 Mb, but ≥9.1 Mg, may have a selective impairment in freedom from distractability. Taken together, our data implicate at least two loci that contribute to a decrement in cognitive function that correlates with deletion size. We propose BSX, a brain homoebox protein, as a candidate gene that is essential for global cognitive function and that haplo-insufficiency of BSX may be necessary and sufficient to cause severe mental retardation. We also propose that deletion of Neurogranin, a gene essential for synapse plasticity and long-term potentiation, contributes to the auditory attention deficit observed in most 11q- patients.

Our data provide important information for genetic counseling with respect to cognitive prognosis, based on deletion size. Specifically, patients with terminal deletion sizes of at least 12.1 Mb are predicted to have severe global cognitive impairment. Patients with terminal deletion sizes 11.8 Mb or smaller are predicted to have much less severe, selective cognitive impairments. Patients with interstitial deletions in distal 11q that span the BSX gene may also have severe cognitive impairment, which we found in a single patient in our cohort that has an interstitial deletion spanning BSX. Future studies will be aimed at determining the role of these candidate genes in the two critical regions in cognitive development and how their deletion contributes to the overall cognitive phenotype in 11q- patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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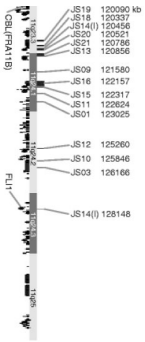

Fig. 1.

q-terminal 16 Mb of chromosome 11. Known RefSeq genes are shown beneath the chromosome bands, and the location of CBL (FRA11B) and FLI1 are indicated. For each of the 14 Jacobsen syndrome patients, the breakpoints were determined by CMA and mapped as indicated. The width of the mark indicating the breakpoint reflects the map distance between the last diploid locus and first haploid locus for each patient. Patient JS14 was determined to have an interstitial deletion between the loci indicated as JS14(I). All other patients exhibited terminal deletions

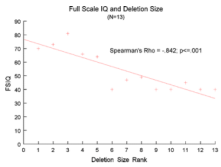

Fig. 2.

Correlation of full-scale IQ and deletion size for the 13 patients with terminal deletions in 11q. Spearman's rho coefficients were calculated to determine the degree of linear association between the ranking of the deletion size and full-scale IQ

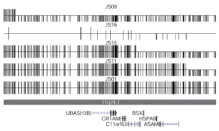

Fig. 3.

The 1.3 Mb region of chromosome 11q24.1 surrounding the 300 kb critical region. Known RefSeq genes are shown beneath the chromosome band. Loci interrogated by chromosomal microarray analysis are indicated by *vertical lines*. Diploid loci extend the full height of the track, while haploid loci extend to the halfway point. Patients JS09, JS16, and JS15 exhibit severe neurocognitive impairment and harbor breakpoints centromeric of the BSX, HSPA8, and ASAM loci. Patients JS11 and JS01 exhibit mild or moderate neurocognitive impairment and breakpoints telomeric of these genes

Table 1

Results of neurocognitive testing on 14 patients for 17 parameters

PT ID	Age (years)	Gender	Deln size	FSIQ	VC	PO	FD	PS	VIQ	PIQ	Info	Sim	Arith	Vocab	Comp	DS	PC	Cd	PA	BD	OA	SS	Mz
JS19	10.4	M	14.3	40	50	50	50	50	46	46	1	1	1	1	1	1	1	1	1	1	1	ND	1
JS18	11.1	F	14	40	50	50	50	50	46	46	1	1	1	1	1	1	1	1	1	1	1	1	1
JS20	19.5	M	13.9	45	50	50	50	54	48	47	1	1	1	1	1	1	1	1	1	1	1	ND	1
JS21	13.8	F	13.7	40	50	50	50	50	46	46	1	1	1	1	1	1	1	1	1	1	1	1	1
JS13	11.2	M	13.6	40	50	50	50	50	46	46	1	1	1	1	1	1	1	1	1	1	ND	1	1
JS09	10.9	M	12.8	49	64	50	50	ND	59	46	4	5	1	3	1	1	1	1	1	1	1	ND	1
JS16	6.8	F	12.4	47	54	50	52	50	50	50	3	1	1	1	1	2	4	1	2	1	1	ND	1
JS15	14.5	M	12.1	40	50	50	50	50	46	46	1	1	1	ND	ND	ND	1	ND	ND	1	ND	ND	ND
JS11	19.8	F	11.8	64	74	65	63	68	68	65	5	7	3	4	6	3	4	3	7	4	2	4	4
JS01	19.1	F	11.4	66	82	62	55	68	73	63	6	8	2	4	8	3	5	4	6	3	4	3	2
JS12	6.7	F	9.1	81	79	90	81	104	74	91	7	6	3	2	9	10	10	10	7	8	8	11	5
JS10	13.8	F	8.6	73	93	56	72	88	89	73	8	11	5	7	9	5	3	7	1	2	4	8	4
JS03	25.3	M	8.2	70	74	72	71	68	73	72	7	5	5	4	5	7	5	4	7	6	4	3	5
JS14	7.6	M	INT	40	50	50	50	50	46	46	1	ND	1	1	ND	ND	1	ND	ND	1	ND	ND	ND

Info Information (school-based fact knowledge), *Sim* Verbal Abstraction (similarities), *Arith* Auditory Math Calculation (arithmetic), *Vocab* Word Knowledge (vocabulary), *Com* Social Reasoning (comprehension), *DS* Auditory Simple Attention (digit span), *PC* Visual Attention (picture completion), *Cd* Psychomotor Speed (coding), *PA* Visual Reasoning (picture arrangement), *BD* Visual-spatial Construction-abstract (block design), *OA* Visual-spatial Construction-concrete (object assembly), *SS* Visual Processing Speed (symbol search), *MZ* Planning/Forethought-usual (mazes), *MR* Visual Reasoning (matrix reasoning), *VIQ* Verbal Intelligence, *PIQ* Performance Intelligence (visual-spatial, synthetic intelligence), *FSIQ* Full-Scale Intelligence (combination of VIQ and PIQ), *VC* Verbal Comprehension Index (purer verbal factor), *PO* Perceptual Organization Index (Purer visual-spatial organization factor), *FD* Freedom from distractability Index, *PS* Processing speed Index, *WM* Working Memory Index