Contents lists available at ScienceDirect

Genomics

journal homepage: www.elsevier.com/locate/ygeno

OMiR: Identification of associations between OMIM diseases and microRNAs

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ARTICLE INFO

Article history: Received 24 June 2010 Accepted 16 October 2010 Available online 23 October 2010

Keywords: miRNAs OMIM diseases

ABSTRACT

A large number of loci for genetic diseases have been mapped on the human genome and a group of hereditary diseases among them have thus far proven unsuccessful to clone. It is conceivable that such "unclonable" diseases are not linked to abnormalities of protein coding genes (PCGs), but of non-coding RNAs (ncRNAs). We developed a novel approach termed OMIR (OMIM and miRNAs), to test whether microRNAs (miRNAs) exhibit any associations with mapped genetic diseases not yet associated with a PCG. We found that "orphan" genetic disease loci were proximal to miRNA loci more frequently than to loci for which the responsible protein coding gene is known, thus suggesting that miRNAs might be the elusive culprits. Our findings indicate that inclusion of miRNAs among the candidate genes to be considered could assist geneticists in their hunt for disease genes, particularly in the case of rare diseases.

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1. Introduction

The Online Mendelian Inheritance in Man database (OMIM, http:// www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM) contains information, including responsible PCGs, phenotypes, linkage data and references, on all human inherited or heritable disorders. Considered a phenotypic companion to the human genome project, and as of August 2010, OMIM comprised 4613 Mendelian diseases (which are prefixed using '#' (n=2837) if the responsible gene is known and with '%' otherwise (n=1776)), 367 genes with an associated phenotype (prefixed using '+'), and 13173 genes (including 183 microRNAs) with known sequence (prefixed using '**).

MicroRNAs (miRNAs) are small RNA molecu'les typically between 19 and 22 nucleotides in length that act as negative regulators of gene expression and are produced from larger primary transcripts (primiRNAs) [1]. In animal cells, miRNAs bind the RNA-induced silencing

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complex (RISC) and specific target messenger RNAs (mRNAs), which either remain untranslated or are degraded [2]. Many investigators have reported that miRNAs are critical in stem cell function [3] and tissue development [4], are involved in viral infections [5] and are associated with oncogenesis [6–9]. Furthermore, we previously reported that miRNAs are frequently located at human Cancer Associated Genomic Regions (CAGRs), such as amplified or deleted regions [10] or mouse modifier loci [11]. Mattick and colleagues recently reported that orthologous miRNA genes are located in CAGRs in human and mouse [12]. However, with the exception of X-linked mental retardation [13], miRNAs have not been thought of as possible causal of Mendelian diseases. To test the hypothesis that some miRNAs could be potentially responsible for a number of "orphan" Mendelian diseases, we developed the OMiR method and used it to conduct a bioinformatics study.

2. Methods

2.1. OMIM Morbid Map

The Morbid Map is an alphabetical list of diseases described in OMIM with their corresponding cytogenetic locations and related mapping studies and references (http://www.ncbi.nlm.nih.gov/ Omim/getmorbid.cgi). We used Morbid Map to extract OMIM identifications (IDs) and corresponding disease names and loci. Information for





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^{0888-7543/\$ -} see front matter © 2010 Elsevier Inc. All rights reserved. doi:10.1016/j.ygeno.2010.10.004



Fig. 1. The five steps of OMiR algorithm: 1) OMIM ID information extraction and conversion; 2) Overlap between miRNAs or Protein Coding Genes loci and OMIM loci; 3) 10,000 randomly reshuffled overlaps, 4) P-value and Q value calculation; and 5) Extraction of the significant overlaps.

diseases labeled using the OMIM IDs and prefixes was converted from cytogenetic location to base position using the UCSC Table Browser (available at http://genome.ucsc.edu/cgi-bin/hgTables, March 2006 release). We focused on: a) entries with a confirmed Mendelian phenotype or phenotypic locus for which the underlying molecular basis is not known (the diseases are prefixed with '%') and b) descriptive entries, usually of a phenotype with known molecular basis that does not represent a unique locus (prefixed with '#'). For statistical purposes, we considered as unknowns the OMIM diseases with a '%' prefix and as controls the '#' prefixed OMIM diseases because the genes responsible for them are known (and are not miRNAs). We examined also the OMIM diseases with prefix '*' (a gene of known sequence) and '+' (a known gene and corresponding phenotype) as controls. If an OMIM ID was associated to more than one locus, each locus was tested separately.

2.2. Extraction and management of miRNA information

The names, chromosome location, start and end positions of 939 miRNAs were downloaded from miRBase release 15.0 (ftp://mirbase.org/pub/mirbase/CURRENT/genomes/hsa.gff). Because each miRNA maps to a much smaller region (about 100 nt) than that mapped to the disease (millions of bp), if two or more miRNAs are significantly associated with an OMIM locus, then they are considered (a posteriori) as a relevant cluster.

2.3. Identifying significant associations of microRNAs and PCGs with OMIM disease loci

For a given OMIM locus, we computed its overlap (i.e. the number of common nucleotides between the miRNAs and the OMIM locus) with the loci of known miRNA transcripts. The probability (p-value) of the observed overlap was computed given the empirical null distribution of overlaps, which was estimated using 10,000 randomly reshuffled versions of the miRNA loci on each chromosome of the genome: each reshuffled set of loci vielded an overlap value, and all these overlaps comprise the empirical null distribution of overlaps. Finally, the false discovery rate (FDR) was calculated by comparing the distribution of p-values against the empirical null distribution of expected p-values, which was estimated using the same 10,000 randomly reshuffled miRNA loci. As before, each reshuffled version yields an overlap value, whose p-value can be computed using the entire set of 10,000 overlap values. All these p-values comprise the empirical null distribution of p-values. This method has been applied to miRNAs and PCGs' transcript loci independently in order to compare the relative number of statistically significant associations obtained. Human ENSEMBL release 54 was used to obtain the PCG loci and miRBase 15.0 to obtain miRNAs loci.

2.4. MiRNA target analysis

A miRNA target analysis was performed to determine if the identified associations could reveal whether the functions of mRNA targets could be related to the associated disease. Using the David Bioinformatics Resources system (http://david.abcc.ncifcrf.gov), we compared the list of terms related to the predicted targeted mRNAs. The terms were evaluated by Bonferroni p-value correction (P<0.05). We evaluated Gene Ontology (biological process, molecular function and cellular component, http://www.geneontology.org/), INTERPRO (http://www.ebi.ac.uk/interpro/), PATHWAY (http://www.biocarta.com/ and http:// www.genome.jp/kegg/), UP_TISSUE (http://david.abcc.ncifcrf.gov/) and SP_PIR_KEYWORDS (functional category) and OMIM disease (http://www.ncbi.nlm.nih.gov/omim/). The predicted targeted mRNAs were retrieved using miRGen (http://www.diana.pcbi.upenn.edu/data/





Fig. 2. Ratios between the percentage of significant OMIM::miRNAs associations and OMIM::mRNAs associations, for each OMIM ID type studied: '%', molecular basis unknown, '#' molecular basis known and '*' and '+', known sequence and/or phenotype.

Table 1

Six significant association between % OMIM IDs and miRNAs.

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OMIM-ID	Description and locus	Expected genes	Associated genes	P-value	Q-value	miRNA symbols	RNA22 and miRGen target terms (David, Bonferroni P<0.05)
%609572	Photoparoxysmal response 2; PPR2; photoparoxysmal response with or without idiopathic generalized epilepsy; gene map locus 13q31.3;	0.92	7	0	0	mir-17 mir-18a mir-19a mir-19b-1 mir-20a mir-622 mir-92a-1	GO: cell death, apoptosis, cell differentiation, cell development, regulation of cellular metabolic process, transmembrane receptor protein tyrosine kinase signaling pathway, anatomical structure morphogenesis, regulation of gene expression, regulation of transcription from RNA; INTERPRO: serine/threonine protein kinase; SP_PIR_KEYWORDS: serine/ threonine-protein kinase; TISSUE: brain, fetal brain.
%300509	Dyslexia, susceptibility to, 9; DYX9; gene map locus Xq27.3; DXS8043	2.88	21	<0.0001	0	mir-506 mir-507 mir-508 mir-509-1 mir- 509-2 mir-509-3 mir-510 mir-513a-1 mir-513a-2 mir-513b mir-513c mir- 514-1 mir-514-2 mir-514-3 mir-888 mir-890 mir-891a mir-891b mir-892a mir-892b	GO: developmental process, anatomical structure development, multicellular organismal development, system development, nervous system development; TISSUE: brain.
%300244	Terminal osseous dysplasia and pigmentary defects; TODPD; gene map locus Xq27.3-q28	7.47	34	<0.0001	0	mir-105-1 mir-105-2 mir-1184 mir- 224 mir-452 mir-506 mir-507 mir-508 mir-509-1 mir-509-2 mir-509-3 mir- 510 mir-513a-1 mir-513a-2 mir-513b mir-513c mir-514-1 mir-514-2 mir- 514-3 mir-767 mir-888 mir-890 mir- 891a mir-891b mir-892a mir-892b	GO: developmental process, anatomical structure development, multicellular organismal development, nervous system development, cellular developmental process, cell differentiation, anatomical structure morphogenesis; UP_SEQ_FEATURE: mutagenesis site; TISSUE: brain, enithelium fetal brain
%300388	Polymicrogyria, Bilateral Perisylvian; BPP; gene map locus Xq27.2-q28; DXS8103 and Xqter	8.52	35	<0.0001	0	mir-105-1 mir-105-2 mir-1184 mir-224 mir-452 mir-506 mir-507 mir-508 mir- 509-1 mir-509-2 mir-509-3 mir-510 mir-513a-1 mir-513a-2 mir-513b mir- 513c mir-514-1 mir-514-2 mir-514-3 mir-767 mir-888 mir-890 mir-891a mir-891b mir-892a mir-892b	GO: cellular component organization and biogenesis, developmental process, anatomical structure development, regulation of biological process, system development, multicellular organismal development, nervous system development, cellular developmental process, cell differentiation, anatomical structure morphogenesis, cell development, synapse; INTERPRO: SRC homology-3, Pleckstrin-like, Pleckstrin homology-type, serine/yhreonine protein kinase; KEGG_PATHWAY: calcium signaling pathway; SP_PIR_KEYWORDS: disease mutation, proto-oncogene, serine/threonine- protein kinase, cytoskeleton, magnesium; UP_SEQ_FEATURE: mutagenesis site; TISSUE: brain, epithelium, fetal brain, melanoma.
%608423	Muscular dystrophy, limb- girdle, type 1F; LGMD1F; gene map locus 7q32.1-q32.2; D7S2544	0.99	6	0	0.01	mir-129-1 mir-182 mir-183 mir-335 mir-593 mir-96	GO: anatomical structure development, developmental process, system development, multicellular organismal development, anatomical structure morphogenesis, organ development, nervous system development, organ morphogenesis; INTERPRO: plekstrin homology-type; SO_PIR_KEYWORDS: cytoskeleton; TISSUE: brain, muscle.
%300614	Deafness, X-linked 5; DFNX5; gene map locus Xq23-q27.3; DXS1220 and DXS8084	22.03	48	<0.0001	0	mir-106a mir-1264 mir-1277 mir- 1298 mir-18b mir-1911 mir-1912 mir- 19b-2 mir-20b mir-220a mir-320d-2 mir-363 mir-424 mir-448 mir-450a-1 mir-450a-2 mir-450b mir-503 mir-504 mir-505 mir-506 mir-507 mir-508 mir-509-1 mir-509-2 mir-509-3 mir- 510 mir-513a-1 mir-513a-2 mir-513b mir-513c mir-514-1 mir-514-2 mir- 514-3 mir-542 mir-766 mir-888 mir- 890 mir-891a mir-891b mir-892a mir- 892b mir-92a-2 mir-934	GO: developmental process, anatomical structure development, system development, multicellular organismal development, cellular developmental process, organ development, cell death, nervous system development, anatomical structure morphogenesis, programmed cell death, apoptosis, regulation of programmed cell death, regulation of programmed cell death, regulation of apoptosis, regulation of gene expression, dephosphorylation; INTERPRO: serine/threonine protein kinase, active site; SP_PIR_KEYWORDS: disease mutation; Tissue: fetal brain.

Table 1	(continued)
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OMIM-ID	Description and locus	Expected genes	Associated genes	P-value	Q-value	miRNA symbols	RNA22 and miRGen target terms (David, Bonferroni P<0.05)
%138900	Uric acid concentration, serum, quantitative trait locus 1; UAQTL1; gout susceptibility 1; gene map locus 4q25; D4S2623	1.14	8	0.0001	0	mir-297 mir-302a mir-302b mir-302c mir-302d mir-367 mir-576	
%152430	Longevity 1; gene map locus 4q25; D4S1564	1.14	8	0.0001	0	mir-297 mir-302a mir-302b mir-302c mir-302d mir-367 mir-576	
%611494	Atrial fibrillation, familial, 5; ATFB5; gene map locus 4q25; rs2200733; rs2200733 and rs10033464	1.14	8	0.0001	0	mir-297 mir-302a mir-302b mir-302c mir-302d mir-367 mir-576	
%610840	Mitral valve prolapse, myxomatous 3; MMVP3; gene map locus 13q31.3-q32.1; D13S132	1.5	7	0	0	mir-17 mir-18a mir-19a mir-19b-1 mir-20a mir-622 mir-92a-1	GO: cell death, apoptosis, cell differentiation, cell development, regulation of cellular metabolic process, transmembrane receptor protein tyrosine kinase signaling pathway, anatomical structure morphogenesis, regulation of gene expression, regulation of transcription from RNA; INTERPRO: serine/ threonine protein kinase; SP_PIR_KEYWORDS: disease mutation, serine/threonine-protein kinase, magnesium, transcription regulation; TISSUE: brain, eye, fetal brain.

public/PublicData/miRGen/v3/Targets/) and RNA22 (http://cbcsrv. watson.ibm.com/rna22.html) with the following parameters: minimum number of paired-up bases in heteroduplex = 12, maximum folding energy for heteroduplex = -25 kcal/mol, maximum number of allowed UN-paired bases = 0 in seed/nucleus of 6 nucleotides.

3. Results

OMiR was implemented in perl and C++. First, we converted the OMIM, miRNAs and PCGs information from cytogenetic regions in base positions corresponding to various locations of OMIM diseases

Table 2

RNA22 folding energy between genes related to %138900, %606460 and %611494 and OmiR associated miRNA clusters.

mRNA	miRNA	Offset	Folding energy (kcal/mol)
gi 146260266 ref NM_001455.3 FOXO3	miR-297	3797 to 3817	-27.00
gi 146260266 ref NM_001455.3 FOXO3	miR-297	6785 to 6805	-26.50
gi 146260269 ref NM_201559.2 FOXO3	miR-297	3770 to 3790	-27.00
gi 146260269 ref NM_201559.2 FOXO3	miR-297	6758 to 6778	-26.50
gi 152963645 ref NM_000325.5 PITX2 3	miR-297	1831 to 1851	-26.40
gi 24234707 ref NM_153426.1 PITX2 2	miR-297	1754 to 1774	-26.40
gi 24234710 ref NM_153427.1 PITX2 1	miR-297	1616 to 1636	-26.40
gi 27894305 ref NM_000576.2 IL1B	miR-297	427 to 447	- 30.00
gi 27894331 ref NM_000877.2 IL1R1	miR-297	672 to 692	-25.20
gi 27894331 ref NM_000877.2 IL1R1	miR-297	4830 to 4850	-29.80
gi 27894331 ref NM_000877.2 IL1R1	miR-297	1036 to 1056	-26.50
gi 27894331 ref NM_000877.2 IL1R1	miR-297	4224 to 4244	-25.50
gi 73622112 ref NM_001223.3 CASP1	miR-297	223 to 243	-25.10
gi 73622114 ref NM_033292.2 CASP1	miR-297	223 to 243	-25.10
gi 146260266 ref NM_001455.3 FOXO3	miR-302a	5946 to 5968	-25.70
gi 146260269 ref NM_201559.2 FOXO3	miR-302a	5919 to 5941	-25.70
gi 208879433 ref NM_183395.2 NLRP3	miR-302a	1807 to 1829	-25.00
gi 208879433 ref NM_183395.2 NLRP3	miR-302a	231 to 253	-26.40
gi 208879434 ref NM_004895.4 NLRP3	miR-302a	1807 to 1829	-25.00
gi 208879434 ref NM_004895.4 NLRP3	miR-302a	231 to 253	-26.40
gi 208879435 ref NM_001127462.2 NLRP3	miR-302a	1807 to 1829	-25.00
gi 208879435 ref NM_001127462.2 NLRP3	miR-302a	231 to 253	-26.40
gi 208879436 ref NM_001127461.2 NLRP3	miR-302a	1841 to 1863	-25.00
gi 208879436 ref NM_001127461.2 NLRP3	miR-302a	265 to 287	-26.40
gi 208879437 ref NM_001079821.2 NLRP3	miR-302a	1199 to 1221	-25.00
gi 27502389 ref NM_001562.2 IL18	miR-302a	997 to 1019	-29.50
gi 73622111 ref NM_033294.2 CASP1	miR-302a	371 to 393	- 34.80
gi 73622112 ref NM_001223.3 CASP1	miR-302a	587 to 609	- 34.80
gi 73622114 ref NM_033292.2 CASP1	miR-302a	650 to 672	- 34.80
gi 73622118 ref NM_033293.2 CASP1	miR-302a	371 to 393	- 34.80
gi 146260266 ref NM_001455.3 FOXO3	miR-302b	5946 to 5968	-25.70
gi 146260269 ref NM_201559.2 FOXO3	miR-302b	5919 to 5941	-25.70
gi 208879433 ref NM_183395.2 NLRP3	miR-302b	1807 to 1829	-25.80
gi 208879433 ref NM_183395.2 NLRP3	miR-302b	231 to 253	-26.40
gi 208879434 ref NM_004895.4 NLRP3	miR-302b	1807 to 1829	-25.80
gi 208879434 ref NM_004895.4 NLRP3	miR-302b	231 to 253	-26.40

Table 2 (continued)

gl20879435jcr[NM_0011274622] NLP29 miR-302b 180 70 1829 -25.80 gl208879435jcr[NM_0011274612] NLP29 miR-302b 184 10 1863 -25.80 gl208879435jcr[NM_0011274612] NLP29 miR-302b 265 for 287 -26.40 gl208879435jcr[NM_0011274612] NLP29 miR-302b 119 to 1221 -25.80 gl27522111[refNM_001522] LL ASP1 miR-302b 97 for 0.193 -35.30 gl7362211[refNM_001522] CASP1 miR-302b 97 for 0.193 -35.30 gl7362211[refNM_001522] CASP1 miR-302b 97 for 0.193 -35.30 gl7362211[refNM_001522] CASP1 miR-302b 97 for 0.174 a.23 -26.60 gl14620265[refNM_001552] FDX03 miR-302c 718 to 733 -25.80 gl14620265[refNM_013252] CNX93 miR-302c 181 to 833 -25.80 gl20887943]refINM_013252 NLP39 miR-302c 181 to 833 -25.80 gl20887943[refINM_00127462] NLP39 miR-302c 180 for 1829 -28.32 gl20887943[refINM_00127462] NLP39 miR-302c 180 for 1829 -28.50 gl20887943[refINM_001127462] NLP39 miR-302c <t< th=""><th>mRNA</th><th>miRNA</th><th>Offset</th><th>Folding energy (kcal/mol)</th></t<>	mRNA	miRNA	Offset	Folding energy (kcal/mol)
g1208579435[ref[NM_0011274622] NLRP3 miR-302b 211 to 253 -26.40 g1208579436[ref[NM_0011274612] NLRP3 miR-302b 2165 to 287 -26.40 g1208579436[ref[NM_0011274612] NLRP3 miR-302b 2165 to 287 -26.40 g1208579436[ref[NM_0011274612] NLRP3 miR-302b 97 to 1019 -36.40 g17362111[ref[NM_001232] CASP1 miR-302b 97 to 1019 -36.40 g17362211[ref[NM_0012323] CASP1 miR-302b 650 to 672 -35.30 g17362211[ref[NM_0012323] CASP1 miR-302b 650 to 672 -35.30 g114620269[ref[NM_001253] FOX03 miR-302c 711 to 393 -25.50 g114620269[ref[NM_001455.3] FOX03 miR-302c 811 to 833 -25.50 g1208579433[ref[NM_183395.2] NLRP3 miR-302c 811 to 833 -25.50 g120857943[ref[NM_001455.4] NLRP3 miR-302c 811 to 833 -25.50 g120857943[ref[NM_001455.4] NLRP3 miR-302c 811 to 833 -25.50 g120857943[ref[NM_001455.4] NLRP3 miR-302c 811 to 833 -25.50 g120857943[ref[NM_001405422] NLRP3 miR-302c 811 to 833	gi 208879435 ref NM_001127462.2 NLRP3	miR-302b	1807 to 1829	-25.80
gl/2087943GrefINM.001127461.2J N.RP3 miR-302b 144 to 1863 -25.80 gl/20887943GrefINM.001762.12J N.RP3 miR-302b 199 to 1221 -25.80 gl/20827943GrefINM.001762.12J N.RP3 miR-302b 199 to 1019 -30.40 gl/2022111refINM.001322.12 IL18 miR-302b 371 to 393 -85.30 gl/2022112refINM.00152.2J CASP1 miR-302b 571 to 609 -35.30 gl/2022113refINM.00152.2J CASP1 miR-302b 571 to 393 -35.30 gl/2022113refINM.00152.2J CASP1 miR-302b 371 to 393 -25.80 gl/2022018refINM.20125.2J CASP1 miR-302c 718 to 7274 -26.60 gl/202879433refINM.183395.2J NLR93 miR-302c 181 to 833 -25.80 gl/208879433refINM.183395.2J NLR93 miR-302c 811 to 833 -25.80 gl/208879431refINM.183395.2J NLR93 miR-302c 811 to 833 -25.80 gl/208879431refINM.18395.2J NLR93 miR-302c 811 to 833 -25.80 gl/208879431refINM.001127462.2J NLR93 miR-302c 811 to 833 -25.80 gl/208879431refINM.001127462.2J NLR93 miR-302c 811 to 833	gi 208879435 ref NM_001127462.2 NLRP3	miR-302b	231 to 253	-26.40
g120879436[ref]NM_001727461.2] NLRP3 miR-302b 255 to 287 - 26.40 g1205879437[ref]NM_001562.2] NLRP3 miR-302b 1199 to 1019 - 30.40 g173622111[ref]NM_001562.2] LLR3 miR-302b 371 to 393 - 35.30 g173622111[ref]NM_001562.2] LLGS1 miR-302b 587 to 609 - 35.30 g17362211[ref]NM_03329.2] CASP1 miR-302b 587 to 609 - 35.30 g17362211[ref]NM_03329.2] CASP1 miR-302b 718 to 723 - 26.60 g1146260259[ref]NM_00159.2] F0X03 miR-302c 718 to 723 - 26.60 g1208879431[ref]NM_183395.2] NLRP3 miR-302c 811 to 833 - 25.80 g1208879431[ref]NM_183395.2] NLRP3 miR-302c 811 to 833 - 25.80 g1208879431[ref]NM_183395.2] NLRP3 miR-302c 811 to 833 - 25.80 g1208879431[ref]NM_001127462.2] NLRP3 miR-302c	gi 208879436 ref NM_001127461.2 NLRP3	miR-302b	1841 to 1863	-25.80
g120879437[ref]NM_00157821.2] NLRP3 miR-302b 197 to 191 -25.80 g173622111[ref]NM_0013234.2] CASP1 miR-302b 371 to 393 -35.30 g173622111[ref]NM_0013234.2] CASP1 miR-302b 560 to 672 -35.30 g173622114[ref]NM_033224.2] CASP1 miR-302b 660 to 672 -35.30 g173622114[ref]NM_033224.2] CASP1 miR-302c 712 to 7234 -26.60 g114620026[ref]NM_01453.5] FNX03 miR-302c 718 to 7234 -26.60 g114620025[ref]NM_014532.5] INXP3 miR-302c 181 to 833 -25.80 g1208879433[ref]NM_183952] NLRP3 miR-302c 181 to 833 -25.80 g1208879433[ref]NM_104395.4] NLRP3 miR-302c 811 to 833 -25.80 g1208879433[ref]NM_004895.4] NLRP3 miR-302c 811 to 833 -25.80 g1208879433[ref]NM_001127462.2] NLRP3 miR-302c 811 to 833 -25.80 g1208879435[ref]NM_001127462.2] NLRP3 miR-302c 1807 to 1829 -28.32 g1208879435[ref]NM_001127462.2] NLRP3 miR-302c 1807 to 1829 -28.30 g1208879435[ref]NM_001127461.2] NLRP3 miR-302c	gi 208879436 ref NM_001127461.2 NLRP3	miR-302b	265 to 287	-26.40
gil2762211 miR-302b 97 to 1019 -30.40 gil73622111 miR-302b 371 to 333 -35.30 gil73622114 miR-302b 587 to 609 -35.30 gil73622114 miR-302b 587 to 609 -35.30 gil73622114 miR-302b 371 to 393 -35.30 gil73622116 miR-302b 371 to 393 -35.30 gil73622116 miR-302c 7185 to 7207 -26.60 gil208879433 miR-302c 180 to 1829 -25.80 gil208879433 miR-302c 180 to 1829 -25.80 gil208879433 miR-302c 180 to 1829 -28.32 gil208879433 miR-302c 180 to 1829 -28.32 gil208879434 miR-302c 180 to 1829 -28.32 gil208879434 miR-302c 180 to 1829 -28.32 gil208879434 miR-302c 180 to 1829 -28.32 gil208879435 miR-302c 180 to 1829 -28.32 gil208879436 miR-302c 281 to 2863 -25.80	gi 208879437 ref NM_001079821.2 NLRP3	miR-302b	1199 to 1221	-25.80
gi[7362211]re[INN.012323.24.2[CASP1 miR-302b 371 to 393 -53.0 gi[73622114[re[INN.012323.2] CASP1 miR-302b 650 to 672 -35.30 gi[73622114[re[INN.033292.2] CASP1 miR-302b 371 to 393 -35.30 gi[73622114]re[INN.033292.2] CASP1 miR-302b 371 to 393 -35.30 gi[146260266]re[INN.201455.3] FOX03 miR-302c 711 to 833 -25.80 gi[20887943]re[INN.183395.2] NLRP3 miR-302c 1817 to 833 -25.80 gi[20887943]re[INN.183395.2] NLRP3 miR-302c 1807 to 1829 -28.32 gi[20887943]re[INN.183395.2] NLRP3 miR-302c 1807 to 1829 -25.50 gi[20887943]re[INN.00147746.2] NLRP3 miR-302c 1807 to 1829 -25.50 gi[20887943]re[INN.00112746.2] NLRP3 miR-302c 1807 to 1829 -25.80 gi[20887943]re[INN.00112746.2] NLRP3 miR-302c 1807 to 1829 -25.80 gi[20887943]re[INN.00112746.2] NLRP3 miR-302c 1807 to 1829 -25.80 gi[20887943]re[INN.00112746.2] NLRP3 miR-302c 281 to 253 -25.80 gi[208879435]re[INN.00112746.2] NLRP3 miR-30	gi 27502389 ref NM_001562.2 IL18	miR-302b	997 to 1019	-30.40
gi73z2112/erflvM_001223.3] CASP1 miR-302b 587 to 609 -35.30 gi73z2114/erflvM_033292.2] CASP1 miR-302b 650 to 672 -35.30 gi73z2114/erflvM_033293.2] CASP1 miR-302c 711 to 393 -26.60 gi73z2114/erflvM_033295.2] CASP1 miR-302c 718 to 7207 -26.60 gi208879433/erflvM_183395.2] NLRP3 miR-302c 811 to 833 -25.80 gi208879433/erflvM_183395.2] NLRP3 miR-302c 231 to 253 -25.50 gi20887943/erflvM_004895.4] NLRP3 miR-302c 811 to 833 -25.80 gi20887943/erflvM_004895.4] NLRP3 miR-302c 810 to 1829 -28.32 gi20887943/erflvM_00112746.2] NLRP3 miR-302c 810 to 1829 -28.32 gi20887943/erflvM_00112746.2] NLRP3 miR-302c 1807 to 1829 -28.32 gi20887943/erflvM_00112746.2] NLRP3 miR-302c 1807 to 1829 -28.32 gi20887943/erflvM_00112746.12 NLRP3 miR-302c 180 to 1863 -25.50 gi20887943/erflvM_00112746.12 NLRP3 miR-302c 190 to 1221 -88.32 gi20887943/jreflvM_00112746.12 NLRP3 miR-302c 18	gi 73622111 ref NM_033294.2 CASP1	miR-302b	371 to 393	- 35.30
gil73622118/efflVM.033292.2[CASP1 miR-302b 650 to 672 -35.30 gil73622118/efflVM.033292.3[CASP1 miR-302b 771 to 393 -35.30 gil7462218/efflVM.033292.3[CASP1 miR-302c 712 to 7234 -26.60 gil746218/efflVM.033295.2] NLRP3 miR-302c 811 to 833 -25.80 gil208879433[reflVM.183395.2] NLRP3 miR-302c 1807 to 1829 -28.32 gil208879433[reflVM.183395.2] NLRP3 miR-302c 1807 to 1829 -25.50 gil208879434[reflVM.004895.4] NLRP3 miR-302c 1807 to 1829 -28.32 gil208879434[reflVM.004895.4] NLRP3 miR-302c 1807 to 1829 -28.52 gil208879435[reflVM.001127462.2] NLRP3 miR-302c 1807 to 1829 -28.32 gil208879435[reflVM.001127462.2] NLRP3 miR-302c 811 to 833 -25.80 gil208879435[reflVM.001127462.2] NLRP3 miR-302c 284 to 867 -25.80 gil208879436[reflVM.001127461.2] NLRP3 miR-302c 265 to 287 -25.80 gil208879437[reflVM.001079821.2] NLRP3 miR-302c 265 to 287 -25.80 gil208879437[reflVM.001079821.2] NLRP3 <t< td=""><td>gi 73622112 ref NM_001223.3 CASP1</td><td>miR-302b</td><td>587 to 609</td><td>- 35.30</td></t<>	gi 73622112 ref NM_001223.3 CASP1	miR-302b	587 to 609	- 35.30
ij12322118[ref]NM_032293.2[CASPI miR-302c 711 to 393 -35.30 ij146202056[ref]NM_01455.3] FOXO3 miR-302c 718 to 7207 -26.60 ij1208879433[ref]NM_183395.2] NLRP3 miR-302c 811 to 833 -25.80 ij208879433[ref]NM_183395.2] NLRP3 miR-302c 231 to 253 -25.50 ij208879433[ref]NM_004895.4] NLRP3 miR-302c 1807 to 1829 -28.32 ij20887943[ref]NM_004895.4] NLRP3 miR-302c 1807 to 1829 -28.32 ij20887943[ref]NM_004895.4] NLRP3 miR-302c 1807 to 1829 -28.32 ij20887943[ref]NM_00112746.2] NLRP3 miR-302c 1807 to 1829 -28.32 ij20887943[ref]NM_00112746.2] NLRP3 miR-302c 1807 to 1829 -28.32 ij20887943[ref]NM_00112746.2] NLRP3 miR-302c 281 to 253 -25.80 ij20887943[ref]NM_00112746.12] NLRP3 miR-302c 265 to 287 -25.80 ij20887943[ref]NM_00172761.2] NLRP3 miR-302c 201 to 253 -25.80 ij20887943[ref]NM_0017281.2] NLRP3 miR-302c 265 to 287 -25.80 ij20887943[ref]NM_0017981.12] NLRP3 miR-302c 57 to 609 -33.20 ij20887943[ref]NM_0017982.1	gi 73622114 ref NM_033292.2 CASP1	miR-302b	650 to 672	- 35.30
gil J42620266 P212 to 7234 -26.60 gil J42620266 PRIND, 201523 PC26.60 gil J42620266 R1 to 833 -25.80 gil Z08879433 PRIND, 183395.21 NLRP3 miR-302c 1807 to 1829 -28.32 gil Z08879433 PRIND, 183395.21 NLRP3 miR-302c 1807 to 1829 -28.32 gil Z08879434 PRIND, 004895.41 NLRP3 miR-302c 181 to 833 -25.80 gil Z08879434 PRIND, 004895.41 NLRP3 miR-302c 181 to 833 -25.80 gil Z08879434 PRIND, 00112746.21 NLRP3 miR-302c 81 to 833 -25.80 gil Z08879435 PRIND, 20112746.21 NLRP3 miR-302c 21 to 253 -25.80 gil Z08879435 PRIND, 00112746.21 NLRP3 miR-302c 21 to 253 -25.80 gil Z08879435 PILRP3 miR-302c 26 to 287 -25.80 gil Z08879436 PRIND, 00112746.12 NLRP3 miR-302c 20 to 252 -25.80 gil Z08879437 PRIND, 00107982.12 NLRP3 miR-302c 19 to 122.1 -28.32 gil Z08879437	gi 73622118 ref NM_033293.2 CASP1	miR-302b	371 to 393	- 35.30
iild2602069[ref]ML201559.2 F0X03 miR-302c 718 5 to 7207 - 26.60 iil208879433]ref]ML_83395.2] NLRP3 miR-302c 811 to 833 - 25.80 iil208879433]ref]ML_83395.2] NLRP3 miR-302c 231 to 253 - 25.50 iil208879434]ref]ML_004895.4] NLRP3 miR-302c 181 to 833 - 25.80 iil208879434]ref]ML_004895.4] NLRP3 miR-302c 1807 to 1829 - 28.32 iil208879434]ref]ML_0014876.4] NLRP3 miR-302c 181 to 833 - 25.80 iil208879435]ref]ML_001127462.2] NLRP3 miR-302c 1807 to 1829 - 28.32 iil208879435]ref]ML_001127462.2] NLRP3 miR-302c 181 to 833 - 25.80 iil208879436]ref]ML_001127462.2] NLRP3 miR-302c 845 to 867 - 25.80 iil208879436]ref]ML_001127461.2] NLRP3 miR-302c 184 to 1863 - 28.32 iil208879436]ref]ML_001172461.2] NLRP3 miR-302c 203 to 225 - 25.80 iil208879437]ref]ML_001079821.2] NLRP3 miR-302c 199 to 121 - 28.32 iil208879437]ref]ML_001079821.2] NLRP3 miR-302c 37 to 393 - 33.20 iil208879437]ref]ML_00107821.2] NLRP3 miR-302c 587 to 609 - 33.20	gi 146260266 ref NM_001455.3 FOXO3	miR-302c	7212 to 7234	-26.60
gil208879433]ref]NU_13395.2] NLRP3 miR-302c 811 to 833 -25.80 gil208879433]ref]NU_13395.2] NLRP3 miR-302c 231 to 253 -25.50 gil208879434]ref]NU_004895.4] NLRP3 miR-302c 8107 to 1829 -28.32 gil208879434]ref]NU_004895.4] NLRP3 miR-302c 8107 to 1829 -28.32 gil208879434]ref]NU_004895.4] NLRP3 miR-302c 811 to 833 -25.80 gil208879434]ref]NU_001127462.2] NLRP3 miR-302c 8107 to 1829 -28.32 gil208879435]ref]NU_001127462.2] NLRP3 miR-302c 8107 to 1829 -28.32 gil208879435]ref]NU_001127462.2] NLRP3 miR-302c 845 to 867 -25.80 gil208879436]ref]NU_001127461.2] NLRP3 miR-302c 265 to 867 -25.80 gil208879436]ref]NU_001127461.2] NLRP3 miR-302c 203 to 225 -25.80 gil208879437]ref]NU_001079821.2] NLRP3 miR-302c 203 to 225 -25.80 gil208879437]ref]NU_001079821.2] NLRP3 miR-302c 307 to 393 -33.20 gil736221141ref]NU_001079821.2] NLRP3 miR-302c 371 to 393 -33.20 gil736221141ref]NU_001079821.2] NLRP3 miR-302c 371 to 393 -33.20	gi 146260269 ref NM_201559.2 FOXO3	miR-302c	7185 to 7207	-26.60
gil208879433]ref]NL_13395.2] NLRP3 miR-302c 1807 to 1829 -28.32 gil208879433]ref]NL_13395.2] NLRP3 miR-302c 231 to 253 -25.50 gil208879434]ref]NL_004895.4] NLRP3 miR-302c 811 to 833 -25.80 gil208879434]ref]NL_004895.4] NLRP3 miR-302c 811 to 833 -25.50 gil208879435]ref]NL_001127462.2] NLRP3 miR-302c 811 to 833 -25.80 gil208879435]ref]NL_001127462.2] NLRP3 miR-302c 811 to 833 -25.50 gil208879435]ref]NL_001127462.2] NLRP3 miR-302c 845 to 867 -25.50 gil208879436]ref]NL_001127461.2] NLRP3 miR-302c 265 to 287 -25.50 gil208879436]ref]NL_001127461.2] NLRP3 miR-302c 265 to 287 -25.50 gil208879437]ref]NL_001127461.2] NLRP3 miR-302c 205 to 287 -25.50 gil208879437]ref]NL_001127461.2] NLRP3 miR-302c 205 to 287 -25.80 gil208879437]ref]NL_001127461.2] NLRP3 miR-302c 199 to 1221 -28.32 gil208879437]ref]NL_001127461.2] NLRP3 miR-302c 199 to 1221 -28.32 gil208879437]ref]NL_001127461.2] NLRP3 miR-302c 199 to 1221 -26.50	gi 208879433 ref NM_183395.2 NLRP3	miR-302c	811 to 833	-25.80
gil20887943]ref]NLM04895.4] NLRP3 mlR-302c 231 to 253 -25.50 gil208879434]ref]NL_004895.4] NLRP3 mlR-302c 110 to 833 -25.80 gil208879434]ref]NL_004895.4] NLRP3 mlR-302c 231 to 253 -25.50 gil208879434]ref]NL_00112746.2] NLRP3 mlR-302c 811 to 833 -25.80 gil208879435]ref]NL_00112746.2] NLRP3 mlR-302c 1807 to 1829 -28.32 gil208879435]ref]NL_00112746.2] NLRP3 mlR-302c 231 to 253 -25.50 gil208879436]ref]NL_00112746.12] NLRP3 mlR-302c 285 to 867 -25.80 gil208879436]ref]NL_00112746.12] NLRP3 mlR-302c 265 to 287 -25.50 gil208879436]ref]NL_00107982.12] NLRP3 mlR-302c 203 to 225 -25.80 gil208879437]ref]NL_00107982.12] NLRP3 mlR-302c 201 to 225 -25.80 gil208879437]ref]NL_00107982.12] NLRP3 mlR-302c 371 to 393 -33.20 gil73622114[ref]NL_00107982.12] NLRP3 mlR-302c 371 to 393 -33.20 gil73622114[ref]NL_00107982.12] NLRP3 mlR-302c 587 to 609 -33.20 gil73622114[ref]NL_001223.3] CASP1 mlR-302c 587 to 609 -33.20 gil	gi 208879433 ref NM_183395.2 NLRP3	miR-302c	1807 to 1829	-28.32
gil208879434[ref]NM_004895.4[NLRP3 miR-302c 811 to 833 -25.80 gil208879434[ref]NM_004895.4[NLRP3 miR-302c 231 to 253 -25.50 gil208879435[ref]NM_001127462.2] NLRP3 miR-302c 181 to 833 -25.80 gil208879435[ref]NM_001127462.2] NLRP3 miR-302c 181 to 833 -25.80 gil208879435[ref]NM_001127462.2] NLRP3 miR-302c 180 to 867 -25.80 gil208879435[ref]NM_001127462.1] NLRP3 miR-302c 184 to 1863 -28.32 gil208879436[ref]NM_001127461.2] NLRP3 miR-302c 184 to 1863 -28.32 gil208879436[ref]NM_001127461.2] NLRP3 miR-302c 265 to 287 -25.50 gil208879437[ref]NM_001079821.2] NLRP3 miR-302c 199 to 1221 -28.32 gil208879437[ref]NM_00179821.2] NLRP3 miR-302c 199 to 1221 -28.32 gil208879437[ref]NM_00179821.2] NLRP3 miR-302c 587 to 609 -33.20 gil73622111[ref]NM_00179821.2] NLRP3 miR-302c 587 to 609 -33.20 gil73622112[ref]NM_001223.3] CASP1 miR-302c 587 to 609 -33.20 gil73622113[ref]NM_001253.3] FOX03 miR-302d 179 to 1781 -26.30	gi 208879433 ref NM_183395.2 NLRP3	miR-302c	231 to 253	-25.50
gil208879434[ref]NM_004895.4] NLRP3 miR-302c 180/ to 1829 -28.32 gil208879435[ref]NM_001127462.2] NLRP3 miR-302c 231 to 253 -25.50 gil208879435[ref]NM_001127462.2] NLRP3 miR-302c 1807 to 1829 -28.32 gil208879435[ref]NM_001127462.2] NLRP3 miR-302c 231 to 253 -25.50 gil208879436[ref]NM_001127461.2] NLRP3 miR-302c 845 to 867 -25.80 gil208879436[ref]NM_001127461.2] NLRP3 miR-302c 265 to 287 -25.50 gil208879437[ref]NM_001127461.2] NLRP3 miR-302c 203 to 225 -25.80 gil208879437[ref]NM_001079821.2] NLRP3 miR-302c 203 to 225 -25.80 gil208879437[ref]NM_001079821.2] NLRP3 miR-302c 97 to 1019 -32.60 gil27502389[ref]NM_0017282.1] NLRP3 miR-302c 97 to 1019 -33.20 gil736221112[ref]NM_001223.3] CASP1 miR-302c 570 to 609 -33.20 gil73622112[ref]NM_0013293.2] CASP1 miR-302c 570 to 672 -33.20 gil146260266[ref]NM_001455.3] FOX03 miR-302d 1759 to 1781 -26.30 gil146260266[ref]NM_001455.3] FOX03 miR-302d 1759 to 1781 -26.30	gi 208879434 ref NM_004895.4 NLRP3	miR-302c	811 to 833	-25.80
gil 2088 7943 [ref]NM_004895.4 [NLRP3 miR-302c 21 to 253 -25.30 gil 2088 79435 [ref]NM_001127462.2 [NLRP3 miR-302c 811 to 833 -25.80 gil 2088 79435 [ref]NM_001127462.2 [NLRP3 miR-302c 21 to 253 -25.80 gil 2088 79435 [ref]NM_001127461.2 [NLRP3 miR-302c 24 to 253 -25.80 gil 2088 79436 [ref]NM_001127461.2 [NLRP3 miR-302c 265 to 867 -25.80 gil 2088 79437 [ref]NM_001127461.2 [NLRP3 miR-302c 265 to 287 -25.80 gil 2088 79437 [ref]NM_00179821.2 [NLRP3 miR-302c 203 to 225 -25.80 gil 2088 79437 [ref]NM_00179821.2 [NLRP3 miR-302c 199 to 121 -28.32 gil 2088 79437 [ref]NM_00179821.2 [NLRP3 miR-302c 371 to 393 -33.20 gil 2088 79437 [ref]NM_00179821.2 [NLRP3 miR-302c 371 to 393 -33.20 gil 2088 79437 [ref]NM_001582.2 [CASP1 miR-302c 587 to 609 -33.20 gil 736221112 [ref]NM_0013293.2 [CASP1 miR-302c 571 to 393 -33.20 gil 74620266 [ref]NM_001455.3 [FOXO3 miR-302d 779 to 1393 -25.80 gil 14620266 [ref]NM_001455.3 [FOXO3 miR-302d 779 to 781 -26.30 <td>gi 208879434 ref NM_004895.4 NLRP3</td> <td>miR-302c</td> <td>1807 to 1829</td> <td>- 28.32</td>	gi 208879434 ref NM_004895.4 NLRP3	miR-302c	1807 to 1829	- 28.32
gil 2088 7943 [ref]NM_001127462.2] NLRP3 miR-302c 811 to 833 -25.80 gil 2088 79435 [ref]NM_001127462.2] NLRP3 miR-302c 231 to 253 -25.50 gil 2088 79436 [ref]NM_001127461.2] NLRP3 miR-302c 845 to 867 -25.80 gil 2088 79436 [ref]NM_001127461.2] NLRP3 miR-302c 265 to 287 -25.50 gil 2088 79436 [ref]NM_001127461.2] NLRP3 miR-302c 205 to 287 -25.50 gil 2088 79437 [ref]NM_001079821.2] NLRP3 miR-302c 205 to 287 -25.80 gil 2088 79437 [ref]NM_00179821.2] NLRP3 miR-302c 205 to 287 -25.80 gil 2088 79437 [ref]NM_00179821.2] NLRP3 miR-302c 207 to 225 -28.32 gil 27502389 [ref]NM_001562.2] L18 miR-302c 371 to 393 -33.20 gil 73622112 [ref]NM_001223.3] CASP1 miR-302c 587 to 609 -33.20 gil 73622118 [ref]NM_0013293.2] CASP1 miR-302c 587 to 609 -33.20 gil 7462014 [ref]NM_001455.3] FOX03 miR-302d 175 to 1781 -26.30 gil 146260266 [ref]NM_001455.3] FOX03 miR-302d 175 to 1781 -26.30 gil 146260266 [ref]NM_001455.3] FOX03 miR-302d 173 to 1754 -26.30	gi 208879434 ref NM_004895.4 NLRP3	miR-302c	231 to 253	- 25.50
gil 2088/9433 [ref]NM_001127462.2] NLRP3 miR-302c 231 to 253 -28.32 gil 208879436 [ref]NM_001127461.2] NLRP3 miR-302c 245 to 267 -25.80 gil 208879436 [ref]NM_001127461.2] NLRP3 miR-302c 265 to 287 -25.80 gil 208879436 [ref]NM_0011727461.2] NLRP3 miR-302c 265 to 287 -25.80 gil 208879437 [ref]NM_001079821.2] NLRP3 miR-302c 203 to 225 -25.80 gil 208879437 [ref]NM_001079821.2] NLRP3 miR-302c 997 to 1019 -32.60 gil 75622111 [ref]NM_001079821.2] NLRP3 miR-302c 997 to 1019 -32.60 gil 73622112 [ref]NM_001562.2] LL8 miR-302c 577 to 609 -33.20 gil 73622112 [ref]NM_0013293.2] CASP1 miR-302c 587 to 609 -33.20 gil 73622113 [ref]NM_0013293.2] CASP1 miR-302c 587 to 609 -33.20 gil 73622114 [ref]NM_0013293.2] CASP1 miR-302c 587 to 609 -33.20 gil 146260266 [ref]NM_001455.3] FOX03 miR-302d 1759 to 1781 -26.30 gil 146260266 [ref]NM_001455.3] FOX03 miR-302d 1759 to 1781 -26.30 gil 146260266 [ref]NM_001455.3] FOX03 miR-302d 4768 to 4790 -29.50	g1/2088/9435/ref/NM_001127462.2/ NLRP3	miR-302c	811 to 833	- 25.80
gil 208879435 [ref]NM_001127461.2] NLRP3 miR-302c 231 to 253 -25.30 gil 208879436 [ref]NM_001127461.2] NLRP3 miR-302c 1841 to 1863 -28.32 gil 208879436 [ref]NM_001127461.2] NLRP3 miR-302c 265 to 287 -25.50 gil 208879437 [ref]NM_001079821.2] NLRP3 miR-302c 203 to 225 -25.80 gil 208879437 [ref]NM_001079821.2] NLRP3 miR-302c 907 to 1019 -32.60 gil 27502389 [ref]NM_001562.2] [L18 miR-302c 977 to 1019 -33.20 gil 73622112 [ref]NM_001223.3] CASP1 miR-302c 587 to 609 -33.20 gil 73622113 [ref]NM_033294.2] CASP1 miR-302c 587 to 609 -33.20 gil 73622114 [ref]NM_033293.2] CASP1 miR-302c 587 to 609 -33.20 gil 74620266 [ref]NM_001455.3] FOXO3 miR-302d 1759 to 1781 -26.30 gil 146260266 [ref]NM_001455.3] FOXO3 miR-302d 5946 to 5968 -27.30 gil 146260266 [ref]NM_001455.3] FOXO3 miR-302d 4741 to 4763 -26.30 gil 146260266 [ref]NM_001455.3] FOXO3 miR-302d 4741 to 4763 -26.30 gil 146260266 [ref]NM_201559.2] FOXO3 miR-302d 5946 to 5968 -27.30 <	g1/208879435/FEFI/NM_001127462.2/ NLRP3	mik-302c	1807 to 1829	- 28.32
gi J208879436 jref[NM_001127461.2] NLRP3IIIIR-302c843 to 867- 25.80gi J208879436 jref[NM_001127461.2] NLRP3miR-302c265 to 287- 25.50gi J208879437 jref[NM_001127461.2] NLRP3miR-302c203 to 225- 25.80gi J208879437 jref[NM_00159821.2] NLRP3miR-302c1199 to 1221- 28.32gi J208879437 jref[NM_001562.2] IL18miR-302c997 to 1019- 32.60gi J73622112 jref[NM_001562.2] IL18miR-302c371 to 393- 33.20gi J73622112 jref[NM_001523.3] CASP1miR-302c587 to 609- 33.20gi J73622114 jref[NM_033293.2] CASP1miR-302c587 to 609- 33.20gi J73622118 jref[NM_033293.2] CASP1miR-302c587 to 609- 33.20gi J46260266 jref[NM_01455.3] FOXO3miR-302d1759 to 1781- 26.30gi J46260266 jref[NM_001455.3] FOXO3miR-302d1759 to 1781- 26.30gi J46260266 jref[NM_001455.3] FOXO3miR-302d5946 to 5968- 27.30gi J46260266 jref[NM_001455.3] FOXO3miR-302d1732 to 1754- 26.30gi J46260266 jref[NM_001455.3] FOXO3miR-302d4741 to 4763- 29.50gi J46260266 jref[NM_011559.2] FOXO3miR-302d5919 to 5941- 27.30gi J46260269 jref[NM_201559.2] FOXO3miR-302d2443 to 2465- 25.10gi J208879433 jref[NM_183395.2] NLRP3miR-302d2443 to 2465- 25.10gi J208879433 jref[NM_183395.2] NLRP3miR-302d3797 to 3819- 26.50gi J208879433 jref[NM_183395.2] NLRP3miR-302d231 to 253-	gi/208879435/FEI/NM_001127462.2/ NLRP3	miR-302c	231 t0 253	- 25.50
gi [208879430]ref[NM_001127461.2] NLRP3miR-302c1641 to 1865- 26.52gi [208879437]ref[NM_001127461.2] NLRP3miR-302c205 to 287- 25.80gi [208879437]ref[NM_001079821.2] NLRP3miR-302c203 to 225- 25.80gi [208879437]ref[NM_001079821.2] NLRP3miR-302c997 to 1019- 32.60gi [73622111]ref[NM_001223.3] CASP1miR-302c371 to 393- 33.20gi [73622112]ref[NM_001223.3] CASP1miR-302c587 to 609- 33.20gi [73622114]ref[NM_0012323] CASP1miR-302c650 to 672- 33.20gi [73622114]ref[NM_001455.3] FOX03miR-302d1759 to 1781- 26.30gi [146260266]ref[NM_001455.3] FOX03miR-302d1754 to 5968- 27.30gi [146260269]ref[NM_001455.3] FOX03miR-302d1732 to 1754- 26.30gi [146260269]ref[NM_001455.3] FOX03miR-302d2474 to 4763- 29.50gi [146260269]ref[NM_001455.3] FOX03miR-302d2443 to 2465- 25.10gi [146260269]ref[NM_001455.3] FOX03miR-302d3797 to 3819- 26.30gi [146260269]ref[NM_001455.3] FOX03miR-302d2443 to 2465- 25.10gi [146260269]ref[NM_011559.2] FOX03miR-302d3797 to 3819- 26.50gi [20887943]ref[NM_183395.2] NLRP3miR-302d3797 to 3819- 26.50gi [20887943]ref[NM_183395.2] NLRP3miR-302d231 to 253- 26.50gi [20887943]ref[NM_183395.2] NLRP3miR-302d231 to 253- 26.50gi [20887943]ref[NM_183395.2] NLRP3miR-302d231 to 253- 26.50	g1/2088/9436/FEI/NM_001127461.2/ NLRP3	mik-302c	845 [0 867 1941 to 1962	- 25.80
gi[208879437]ref[NM_001079821.2] NLRP3 miR-302c 203 to 257 -25.80 gi[208879437]ref[NM_001079821.2] NLRP3 miR-302c 1199 to 1221 -28.32 gi[208879437]ref[NM_001562.2] IL18 miR-302c 997 to 1019 -32.60 gi[73622111]ref[NM_001562.2] IL18 miR-302c 371 to 393 -33.20 gi[73622112]ref[NM_001562.2] CASP1 miR-302c 587 to 609 -33.20 gi[73622114]ref[NM_0013292.2] CASP1 miR-302c 587 to 609 -33.20 gi[73622114]ref[NM_033293.2] CASP1 miR-302c 371 to 393 -33.20 gi[146260266]ref[NM_001455.3] FOX03 miR-302d 1759 to 1781 -26.30 gi[146260266]ref[NM_001455.3] FOX03 miR-302d 4768 to 4790 -29.50 gi[146260266]ref[NM_001455.3] FOX03 miR-302d 5946 to 5968 -27.30 gi[146260266]ref[NM_001455.3] FOX03 miR-302d 1732 to 1754 -26.30 gi[146260266]ref[NM_201559.2] FOX03 miR-302d 5946 to 5968 -27.30 gi[146260266]ref[NM_201559.2] FOX03 miR-302d 5919 to 5941 -27.30 gi[146260266]ref[NM_201559.2] FOX03 miR-302d 5919 to 5941 -27.30 gi[208879	gi/2088/9430/PEI/NM_001127461.2/ NLRP3	miR 202c	1841 to 1863	- 28.32
gi [208879437]ref]NM_001079821.2] NLRP3 miR-302c 129 to 1223 -25.80 gi [208879437]ref]NM_001079821.2] NLRP3 miR-302c 1199 to 1221 -28.32 gi [27502389]ref]NM_001562.2] IL18 miR-302c 997 to 1019 -32.60 gi [73622111]ref]NM_001223.3] CASP1 miR-302c 371 to 393 -33.20 gi [73622114]ref]NM_001223.3] CASP1 miR-302c 587 to 609 -33.20 gi [73622114]ref]NM_03299.2] CASP1 miR-302c 650 to 672 -33.20 gi [73622118]ref]NM_03293.2] CASP1 miR-302c 371 to 393 -33.20 gi [146260266]ref]NM_001455.3] FOXO3 miR-302d 1759 to 1781 -26.30 gi [146260266]ref]NM_001455.3] FOXO3 miR-302d 4768 to 4790 -29.50 gi [146260266]ref]NM_001455.3] FOXO3 miR-302d 1732 to 1754 -26.30 gi [146260266]ref]NM_001455.3] FOXO3 miR-302d 4741 to 4763 -29.50 gi [146260269]ref]NM_01455.3] FOXO3 miR-302d 5946 to 5968 -27.30 gi [146260269]ref]NM_01455.3] FOXO3 miR-302d 5919 to 5941 -26.30 gi [146260269]ref]NM_201559.2] FOXO3 miR-302d 5919 to 5941 -27.30 <td< td=""><td>cil208879450 101 101127401.2 NLRP5</td><td>miR 202c</td><td>203 to 287</td><td>-23.30</td></td<>	cil208879450 101 101127401.2 NLRP5	miR 202c	203 to 287	-23.30
gi[20007943]/ref[NM_001079212] NLRP3 miR-302c 997 to 1019 -32.60 gi[27502389]ref[NM_001562.2] L18 miR-302c 997 to 1019 -32.60 gi[73622111]ref[NM_033294.2] CASP1 miR-302c 587 to 609 -33.20 gi[73622114]ref[NM_033292.2] CASP1 miR-302c 650 to 672 -33.20 gi[73622118]ref[NM_033293.2] CASP1 miR-302c 650 to 672 -33.20 gi[73622118]ref[NM_033293.2] CASP1 miR-302c 371 to 393 -33.20 gi[146260266]ref[NM_001455.3] FOX03 miR-302d 1759 to 1781 -26.30 gi[146260266]ref[NM_001455.3] FOX03 miR-302d 4768 to 4790 -29.50 gi[146260266]ref[NM_001455.3] FOX03 miR-302d 1732 to 1754 -26.30 gi[146260266]ref[NM_001455.3] FOX03 miR-302d 1732 to 1754 -26.30 gi[146260266]ref[NM_201559.2] FOX03 miR-302d 4741 to 4763 -29.50 gi[146260269]ref[NM_201559.2] FOX03 miR-302d 5919 to 5941 -27.30 gi[208879433]ref[NM_183395.2] NLRP3 miR-302d 2443 to 2465 -25.10 gi[208879433]ref[NM_183395.2] NLRP3 miR-302d 3797 to 3819 -26.50 gi[208879433]re	gi/2000/943//101/101/0010/9021.2/ NLRP3	miP 202c	203 t0 223	-23.80
gi[7302363]ref]NM_00122.2] IL18 miR-302c 357 to 1015 - 32.00 gi[73622111]ref]NM_0033294.2] CASP1 miR-302c 371 to 393 - 33.20 gi[73622112]ref]NM_001223.3] CASP1 miR-302c 587 to 609 - 33.20 gi[73622114]ref]NM_033293.2] CASP1 miR-302c 587 to 609 - 33.20 gi[73622118]ref]NM_033293.2] CASP1 miR-302c 371 to 393 - 33.20 gi[73622118]ref]NM_001455.3] FOX03 miR-302d 1759 to 1781 - 26.30 gi[146260266]ref]NM_001455.3] FOX03 miR-302d 4768 to 4790 - 29.50 gi[146260266]ref]NM_001455.3] FOX03 miR-302d 5946 to 5968 - 27.30 gi[146260266]ref]NM_01455.3] FOX03 miR-302d 5946 to 5968 - 27.30 gi[146260269]ref]NM_201559.2] FOX03 miR-302d 1732 to 1754 - 26.30 gi[146260269]ref]NM_201559.2] FOX03 miR-302d 5919 to 5941 - 27.30 gi[208879433]ref]NM_183395.2] NLRP3 miR-302d 5919 to 5941 - 27.30 gi[208879433]ref]NM_183395.2] NLRP3 miR-302d 3797 to 3819 - 26.50 gi[208879433]ref]NM_183395.2] NLRP3 miR-302d 231 to 253 - 26.50 gi[20	gil200075457 [10][10][10][01075621.2] [10][10] gil27502280[rof]NIM_0015622] [119	miP 202c	1155 t0 1221	22.60
gi J 3022111 [ref[NM_03293:2] [CASP1 miR-302c 587 to 609 -33.20 gi J 3622112 [ref]NM_03293.2] [CASP1 miR-302c 650 to 672 -33.20 gi J 3622114 [ref]NM_033293.2] [CASP1 miR-302c 371 to 393 -33.20 gi J 3622118 [ref]NM_001455.3] FOXO3 miR-302c 371 to 393 -33.20 gi J 46260266 [ref]NM_001455.3] FOXO3 miR-302d 1759 to 1781 -26.30 gi J 46260266 [ref]NM_001455.3] FOXO3 miR-302d 5946 to 5968 -27.30 gi J 146260266 [ref]NM_001455.3] FOXO3 miR-302d 5946 to 5968 -27.30 gi J 146260269 [ref]NM_201559.2] FOXO3 miR-302d 1732 to 1754 -26.30 gi J 146260269 [ref]NM_201559.2] FOXO3 miR-302d 4741 to 4763 -29.50 gi J 146260269 [ref]NM_201559.2] FOXO3 miR-302d 5919 to 5941 -27.30 gi J 146260269 [ref]NM_201559.2] FOXO3 miR-302d 5919 to 5941 -27.30 gi J 208879433]ref]NM_183395.2] NLRP3 miR-302d 2443 to 2465 -25.10 gi 208879433]ref]NM_183395.2] NLRP3 miR-302d 3797 to 3819 -26.50 gi 208879433]ref]NM_183395.2] NLRP3 miR-302d 231 to 253 -26.50	gi[27502505][E1]NM_0320042] CASP1	miR-302c	371 to 393	- 32.00
gil/3622114[rtel]NM_031292.2] CASP1 miR-302c 650 to 672 -33.20 gil/3622114[rtel]NM_033292.2] CASP1 miR-302c 650 to 672 -33.20 gil/3622118[rtel]NM_033292.2] CASP1 miR-302c 371 to 393 -33.20 gil/3622118[rtel]NM_033293.2] CASP1 miR-302c 650 to 672 -33.20 gil/146260266[rtel]NM_001455.3] FOX03 miR-302d 1759 to 1781 -26.30 gil/146260266[rtel]NM_001455.3] FOX03 miR-302d 5946 to 5968 -27.30 gil/146260266[rtel]NM_001455.3] FOX03 miR-302d 5946 to 5968 -27.30 gil/146260269[rtel]NM_201559.2] FOX03 miR-302d 1732 to 1754 -26.30 gil/146260269[rtel]NM_201559.2] FOX03 miR-302d 4741 to 4763 -29.50 gil/146260269[rtel]NM_201559.2] FOX03 miR-302d 5919 to 5941 -27.30 gil/208879433]rtel]NM_183395.2] NLRP3 miR-302d 2443 to 2465 -25.10 gil/208879433]rtel]NM_183395.2] NLRP3 miR-302d 3797 to 3819 -26.50 gil/208879433]rtel]NM_183395.2] NLRP3 miR-302d 231 to 253 -26.50 gil/208879433[rtel]NM_004895.4] NLRP3 miR-302d 2443 to 2465 -25.10	gi[73622111]ref[NM_0012233] CASP1	miR-302c	587 to 609	- 33.20
gi[73622118]ref[NM_033293.2] CASP1 miR-302c 371 to 393 -33.20 gi[73622118]ref[NM_033293.2] CASP1 miR-302c 371 to 393 -26.30 gi[146260266]ref[NM_001455.3] FOX03 miR-302d 4768 to 4790 -29.50 gi[146260266]ref[NM_001455.3] FOX03 miR-302d 5946 to 5968 -27.30 gi[146260266]ref[NM_001455.3] FOX03 miR-302d 1732 to 1754 -26.30 gi[146260269]ref[NM_201559.2] FOX03 miR-302d 1732 to 1754 -26.30 gi[146260269]ref[NM_201559.2] FOX03 miR-302d 4741 to 4763 -29.50 gi[146260269]ref[NM_201559.2] FOX03 miR-302d 5919 to 5941 -27.30 gi[146260269]ref[NM_201559.2] FOX03 miR-302d 5919 to 5941 -25.10 gi[208879433]ref[NM_183395.2] NLRP3 miR-302d 2443 to 2465 -25.10 gi[208879433]ref[NM_183395.2] NLRP3 miR-302d 3797 to 3819 -26.50 gi[208879433]ref[NM_183395.2] NLRP3 miR-302d 231 to 253 -26.50 gi[208879434]ref[NM_004895.4] NLRP3 miR-302d 2443 to 2465 -25.10 gi[208879434]ref[NM_004895.4] NLRP3 miR-302d 2443 to 2465 -26.50	gi[73622112]ref[NM_032922] CASP1	miR-302c	650 to 672	- 33.20
gi 146260266 ref NM_001455.3] FOX03 miR-302d 1759 to 1781 -26.30 gi 146260266 ref NM_001455.3] FOX03 miR-302d 4768 to 4790 -29.50 gi 146260266 ref NM_001455.3] FOX03 miR-302d 5946 to 5968 -27.30 gi 146260269 ref NM_201559.2] FOX03 miR-302d 1732 to 1754 -26.30 gi 146260269 ref NM_201559.2] FOX03 miR-302d 4741 to 4763 -29.50 gi 146260269 ref NM_201559.2] FOX03 miR-302d 5919 to 5941 -26.30 gi 208879433 ref NM_183395.2] NLRP3 miR-302d 2443 to 2465 -25.10 gi 208879433 ref NM_183395.2] NLRP3 miR-302d 3797 to 3819 -26.50 gi 208879433 ref NM_183395.2] NLRP3 miR-302d 231 to 253 -26.50 gi 208879433 ref NM_004995.4 NLRP3 miR-302d 2443 to 2465 -25.10	gi[73622118]ref[NM_033293.2] CASP1	miR-302c	371 to 393	- 33 20
gil 146260266[ref]NM_001455.3] FOX03 miR-302d 4768 to 4790 -29.50 gil 146260266[ref]NM_001455.3] FOX03 miR-302d 5946 to 5968 -27.30 gil 146260266]ref]NM_201559.2] FOX03 miR-302d 1732 to 1754 -26.30 gil 146260269[ref]NM_201559.2] FOX03 miR-302d 4741 to 4763 -29.50 gil 146260269[ref]NM_201559.2] FOX03 miR-302d 5919 to 5941 -26.30 gil 208879433[ref]NM_183395.2] NLRP3 miR-302d 5919 to 5941 -27.30 gil 208879433[ref]NM_183395.2] NLRP3 miR-302d 2443 to 2465 -25.10 gil 208879433[ref]NM_183395.2] NLRP3 miR-302d 231 to 253 -26.50 gil 208879433[ref]NM_004895.4] NLRP3 miR-302d 2443 to 2465 -25.10	gil1462602661refINM_00145531 F0X03	miR-302d	1759 to 1781	-26.30
gi 146260266 ref[NM_001455.3] FOX03 miR-302d 5946 to 5968 -27.30 gi 146260269 ref[NM_201559.2] FOX03 miR-302d 1732 to 1754 -26.30 gi 146260269 ref[NM_201559.2] FOX03 miR-302d 4741 to 4763 -29.50 gi 146260269 ref[NM_201559.2] FOX03 miR-302d 5919 to 5941 -27.30 gi 208879433]ref[NM_183395.2] NLRP3 miR-302d 2443 to 2465 -25.10 gi 208879433]ref[NM_183395.2] NLRP3 miR-302d 231 to 253 -26.50 gi 208879433]ref[NM_183395.2] NLRP3 miR-302d 2443 to 2465 -25.10 gi 208879433]ref[NM_183395.2] NLRP3 miR-302d 231 to 253 -26.50 gi 208879433]ref[NM_004895.4] NLRP3 miR-302d 2443 to 2465 -25.10	gi 146260266 ref NM_001455.3 FOXO3	miR-302d	4768 to 4790	-29.50
gi 146260269 ref NM_201559.2 FOX03miR-302d1732 to 1754-26.30gi 146260269 ref NM_201559.2 FOX03miR-302d4741 to 4763-29.50gi 146260269 ref NM_201559.2 FOX03miR-302d5919 to 5941-27.30gi 208879433 ref NM_183395.2 NLRP3miR-302d2443 to 2465-25.10gi 208879433 ref NM_183395.2 NLRP3miR-302d3797 to 3819-26.50gi 208879433 ref NM_183395.2 NLRP3miR-302d231 to 253-26.50gi 208879434 ref NM_004895.4 NLRP3miR-302d2443 to 2465-25.10	gil146260266lrefINM 001455.3l FOXO3	miR-302d	5946 to 5968	-27.30
gi 146260269 ref NM_201559.2 FOX03miR-302d4741 to 4763-29.50gi 146260269 ref NM_201559.2 FOX03miR-302d5919 to 5941-27.30gi 208879433 ref NM_183395.2 NLRP3miR-302d2443 to 2465-25.10gi 208879433 ref NM_183395.2 NLRP3miR-302d3797 to 3819-26.50gi 208879433 ref NM_183395.2 NLRP3miR-302d231 to 253-26.50gi 208879434 ref NM_004895.4 NLRP3miR-302d2443 to 2465-25.10	gi 146260269 ref NM_201559.2 FOXO3	miR-302d	1732 to 1754	-26.30
gi 146260269 ref NM_201559.2 FOXO3miR-302d5919 to 5941-27.30gi 208879433 ref NM_183395.2 NLRP3miR-302d2443 to 2465-25.10gi 208879433 ref NM_183395.2 NLRP3miR-302d3797 to 3819-26.50gi 208879433 ref NM_183395.2 NLRP3miR-302d231 to 253-26.50gi 208879434 ref NM_004895.4 NLRP3miR-302d2443 to 2465-25.10	gi 146260269 ref NM_201559.2 FOXO3	miR-302d	4741 to 4763	-29.50
gi[208879433]ref[NM_183395.2] NLRP3miR-302d2443 to 2465- 25.10gi[208879433]ref[NM_183395.2] NLRP3miR-302d3797 to 3819- 26.50gi[208879433]ref[NM_183395.2] NLRP3miR-302d231 to 253- 26.50gi[208879434]ref[NM_004895.4] NLRP3miR-302d2443 to 2465- 25.10	gi 146260269 ref NM_201559.2 FOXO3	miR-302d	5919 to 5941	-27.30
gi[208879433]ref[NM_183395.2] NLRP3 miR-302d 3797 to 3819 - 26.50 gi[208879433]ref[NM_183395.2] NLRP3 miR-302d 231 to 253 - 26.50 gi[208879434]ref[NM_004895.4] NLRP3 miR-302d 2443 to 2465 - 25.10	gi 208879433 ref NM_183395.2 NLRP3	miR-302d	2443 to 2465	-25.10
gi[208879433]ref[NM_183395.2] NLRP3 miR-302d 231 to 253 -26.50 gi[208879434]ref[NM_004895.4] NLRP3 miR-302d 2443 to 2465 -25.10	gi 208879433 ref NM_183395.2 NLRP3	miR-302d	3797 to 3819	-26.50
gi 208879434 ref NM_004895.4 NLRP3 miR-302d 2443 to 2465 -25.10	gi 208879433 ref NM_183395.2 NLRP3	miR-302d	231 to 253	-26.50
	gi 208879434 ref NM_004895.4 NLRP3	miR-302d	2443 to 2465	-25.10
gi 208879434 ret NM_004895.4 NLRP3 miR-302d 4139 to 4161 - 26.50	gi 208879434 ref NM_004895.4 NLRP3	miR-302d	4139 to 4161	-26.50
gi]208879434/ref]NM_004895.4 NLRP3 miR-302d 231 to 253 -26.50	gi 208879434 ref NM_004895.4 NLRP3	miR-302d	231 to 253	-26.50
gi]208879435 ref NM_001127462.2 NLRP3 miR-302d 2443 to 2465 -25.10	gi 208879435 ref NM_001127462.2 NLRP3	miR-302d	2443 to 2465	-25.10
gi]208879435 ref NM_001127462.2 NLRP3 miR-302d 3968 to 3990 - 26.50	gi 208879435 ref NM_001127462.2 NLRP3	miR-302d	3968 to 3990	-26.50
gi]208879435 ref NM_001127462.2 NLRP3 miR-302d 231 to 253 - 26.50	gi 208879435 ref NM_001127462.2 NLRP3	miR-302d	231 to 253	-26.50
gi]208879436 ref NM_001127461.2 NLRP3 miR-302d 2477 to 2499 - 25.10	gi 208879436 ref NM_001127461.2 NLRP3	miR-302d	2477 to 2499	-25.10
gi]208879436 ref NM_001127461.2 NLRP3 miR-302d 4002 to 4024 - 26.50	gi 208879436 ref NM_001127461.2 NLRP3	miR-302d	4002 to 4024	-26.50
gi]208879436 ref NM_001127461.2 NLRP3 miR-302d 265 to 287 - 26.50	gi 208879436 ref NM_001127461.2 NLRP3	miR-302d	265 to 287	-26.50
gi[208879437]rtt[NM_001079821.2] NLRP3 miR-302d 1835 to 1857 -25.10	gi 208879437 ref NM_001079821.2 NLRP3	miR-302d	1835 to 1857	-25.10
gl/2088/943/jretjNM_0U10/9821.2J NLRP3 mik-302d 3531 to 3553 -26.50	gi/2088/9437/ret/NM_001079821.2 NLRP3	mik-302d	3531 to 3553	- 26.50
gl2/502389/ret/NM_001562.2/ IL18 miR-302d 997 to 1019 -28.50	gi[27502389]ret[NM_001562.2] IL18	miR-302d	997 to 1019	- 28.50
g1/36/2111/retINM_03294.21 (ASP1 mik-302d 371 to 393 -33.30 mik-302d 371 to 393 -33.30	gi/3622111/ref/NM_033294.2/ CASP1	mik-302d	3/1 to 393	- 33.30
gtj/3622112[ret]tNr_U01223.3] CASP1 mik-302d 587 to 609 -33.30	gi/3622112/ref/NM_001223.3/ CASP1	mik-302d	587 to 609	- 33.30
gl/3622114[ref[NM_03292.2] CASP1 miR-302d b50 to b/2 -33.30	gi /3622114 ref NM_033292.2 CASP1	mik-302d	650 to 6/2	- 33.30
gij/3022116jiteljiNiv_U52255.2[CASP1 mik-5020 3/10.393 -33.30	gi/ عدد الااترانية: الااترانية: الالالال2013، 243.24 CASPI	1111K-3U20	3/1 10 393	- 33.30
צוןביססיאססדון בוויזאיבטטטסיו. בן וגואו וווא אויבטעסיו. בן וגואו ווואיסירטע באטט געער איז אויבער איז אויבער איז באטער באט גער גער איז גער	צון 2.7,20111111111111111111111111111111111111	шк-этс-эр	2003 10 2024	-23.20

and genes. Then, we calculated the associations between miRNAs or clusters of miRNAs or mRNAs and OMIM diseases loci and finally validated these through permutations. The five steps of OMiR are presented in the Fig. 1. Out of the total number of associations, at 1% FDR (false discovery rate) we found 5.06%, 8.46% and 10.15% significant associations (P<0.05) between miRNAs and OMIM IDs '*' or '+', between miRNAs and the '#' prefixed OMIM diseases and miRNAs and the OMIM diseases with a '%' prefix, respectively.

The percentages of associations with mRNAs, in the same OMIM IDs categories were 48.25% ('*' or '+'), 52.45% ('#') and 38.55% ('%') respectively. Based on the generalized hypothesis of 10,000 available associations, the Fisher exact test between the categories '#' and '%' was P<0.001, while using all three categories was P<0.001 (Fig. 2). Table 1 reports the significant associations between 10 "orphan" diseases and 6 miRNAs clusters containing 63 miRNAs in total (6.7% of the human

miRNAs from miRBase 15.0), (Supplemental file MiRNAs_OMIM_Associations.xls reports all found 88 significant associations).

Then we explored for 6 of the 88 significant '%' associated miRNAs the mRNAs target terms using DAVID (http://david.abcc.ncifcrf.gov/) (Table S1; the complete lists of significant target terms are reported in Supplemental Materials (Table S2–S7 for RNA22 predicted targets and file miRGen_DAVID.zip for miRGen predicted targets)). In several instances, the related Gene Ontology, INTERPRO, PATHWAY, UP_TIS-SUE and SP_PIR_KEYWORDS functional terms were indeed relevant for the claimed associated disease. Table 1 shows the significant associations obtained for miRNAs associated with '%' by statistical validation using 10,000 permutations (P<0.05, FDR<1%). For example, the cluster miR-297, miR-302a, miR-302b, miR-302c, miR-302d, miR-367, miR-376 is significantly associated by OMiR to UAQTL1 (uric acid concentration serum, quantitative trait locus 1), gout

susceptibility 1, longevity 1 and ATFB5 (atrial fibrillation familial 5) loci, all located in 4q25 chromosomal region. Experimentally, several PCGs were already found to be involved in the pathogenesis of these disorders, but none in a causal association: CPPD, CASP1, NALP3, IL-1B and IL1R for UAQTL1 disease, FOXO3A for longevity and PITX2 for atrial fibrillation. RNA22 predicted that miR-297 targets FOXO3, PITX2, IL1B, IL1R, IL18 and CASP1; miR-302a/b/c/d targets FOXO3, NLRP3 and CASP1 and miR-576-3p targets IL1R (Table 2).

4. Discussion

Traditionally, Mendelian disorders have been classified as recessive or dominant and by OMIM based on type of known information about them. However, there is increasing recognition that these classifications can be explored to find possible candidate for "orphan" diseases. Here, we investigated the possible association of miRNAs with human "orphan" diseases. We found 43 miRNA clusters consisting of about 37.2% (n = 349) of all known miRNAs and located in 80 OMIM '%' loci. The diseases we found significantly associated with the clusters of miRNAs are either associated to a locus, one or more markers and for few of them, several involved genes are known. For six of them we presented a functional study as a result of the integrated analysis of different functional databases (e.g. GO, KEGG pathways, SP-PIR keywords) provided interesting biological support to OMiR findings. As the number of individuals affected by inherited Mendelian disorders, excluding cancers, are usually small and therefore the available samples limited, OMIR can be a useful companion to the scientists for focusing on interesting culprit genes. Furthermore, with the identification of other categories of ncRNAs OMiR algorithm can be re-run for identification of further new possible "protein-less" non-coding culprits.

Our efforts to identify miRNAs important for diseases without known pathogeny are not isolated. Recently two papers have been published with the aim to evaluate human diseases and miRNAs genomic region associations. Lu and colleagues by manually curating the published associations, built a human miRNA associated disease network, suggesting that the applied method can be used in the future to discover novel disease associations [14]. By using a panel of singlenucleotide polymorphisms in miRNAs, Muiños-Gimeno and colleagues identified two miRNA regions showing geographical allelic frequency variation among four HapMAp populations [15]. None of these studies applied and compared the same method to a large scale of diseases already associated with a responsible gene or miRNA and "orphan" disease as we present with OmiR.

5. Conclusion

We devised and implemented OMiR, an algorithm to compute and study the associations between miRNAs and genetic diseases. We took advantage of the OMIM database to retrieve disease information. Additional association options can be implemented to extend the reach of OMiR, such as the possibility of using markers known by the user that have not yet been published. Moreover, updating OMiR with new OMIM IDs and new miRNAs will increase the robustness of the assay. Our work represents a novel way to extract information on the relationships between miRNAs and diseases with OMIM IDs not associated with a specific disease gene.

Supplementary materials related to this article can be found online at doi:10.1016/j.ygeno.2010.10.004.

Acknowledgments

We thank National Institutes of Health and Online Mendelian Inheritance in Man, OMIM™, URL: http://www.ncbi.nlm.nih.gov/omim/ for the available information at ftp://ftp.ncbi.nih.gov/repository/OMIM/. We thank Angelique Geehan, ESL, Department of Scientific Publications, The University of Texas MD Anderson Cancer Center, for expert editorial assistance.

Funding: GAC was supported as a Fellow of The University of Texas M. D. Anderson Research Trust, a Fellow of The University of Texas System Regents Research Scholar, and by the Ladjevardian Regents Research Scholar Fund. Work in Dr Calin's laboratory is supported in part by NIH/NCI, DOD and by 2009 Seena Magowitz – Pancreatic Cancer Action Network – AACR Pilot Grant.

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