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Runs of homozygosity in spontaneous abortions from families with recurrent pregnancy loss

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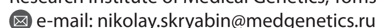

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Recurrent pregnancy loss (RPL) is a severe reproductive pathology with a significant component of unexplained etiology. Extended homozygous regions as a possible etiological factor for RPL were sought in the genomes of embryos. Twenty-two paired first-trimester spontaneously aborted embryos from eleven women with recurrent miscarriage were analyzed. All embryos had normal karyotypes according to metaphase karyotyping and conventional comparative genomic hybridization. SurePrint G3 Human CGH + SNP 4 × 180K microarrays (Agilent Technologies) were used to search for homozygous regions. As a result, 39 runs of homozygosity (ROH) were identified in extraembryonic tissues of 15 abortuses. Verification of recurrent homozygous regions was performed by Sanger sequencing. The presence of occasional heterozygous SNPs was shown in 25 extended ROHs, which may indicate that they did not arise *de novo* but were inherited from parents. In the course of inheritance in a series of generations, they may accumulate mutations, leading to heterozygosity for several sites in the initially homozygous population-specific regions. Homozygotization of recessive mutations is one of the putative mechanisms of the influence of such inherited ROHs on RPL development. The high frequency of extended ROHs detected in the present study may point to a role of inbreeding in RPL etiology. Homozygous regions may also occur due to uniparental disomy, and abnormalities of genomic imprinting may be another mechanism responsible for the pathological manifestation of ROHs in embryogenesis. Indeed, five predicted imprinted genes were identified within ROHs according to the Geneimprint database: *OBSCN*, *HIST3H2BB*, *LMX1B*, *CELF4*, and *FAM59A*. This work reports the first finding of a high frequency of extended ROHs in spontaneously aborted embryos with normal karyotypes from families with RPL.
Key words: recurrent pregnancy loss; array-based comparative genomic hybridization; runs of homozygosity; spontaneous abortions; genomic imprinting.

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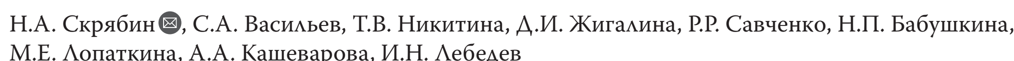
Районы гомозиготности в тканях абортусов из семей с привычным невынашиванием беременности



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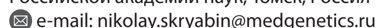

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Привычное невынашивание беременности является тяжелой репродуктивной патологией, при этом почти в половине случаев его этиология остается невыясненной. В настоящей работе проведено исследование протяженных гомозиготных районов (runs of homozygosity – ROH) в геноме как возможного этиологического фактора в развитии привычного невынашивания беременности. Всего проанализировано 22 парных абортуса первого триместра беременности от 11 женщин с привычным невынашиванием беременности. У всех абортусов был нормальный кариотип по результатам метафазного кариотипирования и сравнительной геномной гибридизации на метафазных пластинках. Для поиска гомозиготных регионов были использованы микрочипы SurePrint G3 Human CGH + SNP 4 × 180K (Agilent Technologies). В результате в экстраэмбриональных тканях 15 абортусов выявлены 39 гомозиготных областей. Для образцов с повторяющимися ROH была проведена верификация с помощью секвенирования по Сэнгеру. Для 25 протяженных ROH было показано наличие единичных гетерозиготных SNP, что может свидетельствовать в пользу того, что они образуются не *de novo*, а наследуются от родителей. При этом в ходе наследования в ряду поколений в них могут накапливаться мутации, приводящие к гетерозиготизации изначально гомозиготных участков генома. Один из возможных механизмов влияния таких унаследованных ROH на патогенез привычного невынашивания беременности – гомозиготизация рецессивных мутаций. Высокая частота длинных ROH, обнаруженная в настоящем исследовании, указывает на роль инбридинга в этиологии привычного невынашивания беременности. Гомозиготные области

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могут возникать также из-за однородительской дисомии, следовательно, аномалии геномного импринтинга могут быть другим механизмом, ответственным за патологическое проявление гомозиготных районов в эмбриогенезе. В составе обнаруженных регионов гомозиготности в соответствии с базой данных Geneimprint было выявлено пять предположительно импринтированных генов: *OBSCN*, *HIST3H2BB*, *LMX1B*, *CELF4* и *FAM59A*. В результате проведенного исследования впервые показана высокая частота длинных ROH в тканях спонтанных абортусов с нормальным кариотипом из семей с привычным невынашиванием беременности.
Ключевые слова: привычное невынашивание беременности; сравнительная геномная гибридизация на микрочипах; районы гомозиготности; ROH; спонтанные аборты; геномный импринтинг.

Introduction

Spontaneous abortions occur in approximately 15 % of pregnancies in different populations; however, in some families, pregnancy loss occurs more than once (Nikitina et al., 2016). According to the guidelines of the European Society of Human Reproduction and Embryology, a diagnosis of recurrent pregnancy loss (RPL) should be considered after the loss of two or more pregnancies (Goddijn, 2017). The prevalence of RPL varies from 2 to 5 % of the total number of pregnancies (El Hachem et al., 2017). Recurrent pregnancy loss may be caused by uterine abnormalities, parental chromosomal aberrations, antiphospholipid antibodies, polycystic ovarian syndrome, diabetes mellitus, and hyperthyroidism. In about half of all cases, the RPL cause remains unexplained (Nikitina et al., 2016).

Homozygotization of recessive mutations due to runs of homozygosity (ROH) or uniparental disomy (UPD) may be one of the causes (Robberecht et al., 2012; Niida et al., 2018). In a consanguine marriage with manifestations of recessive diseases, the homozygous risk locus is likely to fall into an extended homozygous region. Thus, pathogenic recessive variants can be identified in affected individuals from inbred population by identifying ROHs. This approach to the search for pathological mutations made it possible to map genes associated with many recessive Mendelian diseases (Botstein, Risch, 2003).

The emergence of regions with ROHs may result from inbreeding, but ROHs are found in human genomes even among outbred populations (Ceballos et al., 2018). Population history and cultural factors may influence homozygosity levels, and therefore ROHs are characterized by population specificity, while data on their prevalence in Russian populations are unavailable yet.

The aim of this paper was to study the role of homozygotization of various genome regions in the pathogenesis of RPL.

Materials and methods

Patients supervised by the Laboratory of Cytogenetics of the Research Institute of Medical Genetics (Tomsk, Russia) from 1987 to 2018 were analyzed. Material from first-trimester spontaneously aborted embryos was obtained from gynecologic and obstetric clinics in Tomsk and Seversk (Russia). Information was recorded about the maternal and paternal age, gynecological anamnesis of the women, the number and outcomes of previous pregnancies, and features of the present gestation.

Tissue samples obtained by curettage were transferred to the cytogenetic laboratory in sterile saline. The products of conception were examined, and extraembryonic tissues were separated from decidua and blood clots. All abortuses had normal karyotypes according to the results of metaphase karyotyping and conventional comparative genomic hybridization of extraembryonic tissues. For conventional karyotyping, metaphase chromosomes were obtained after long-term culture of fibroblasts of extraembryonic mesoderm in DMEM/F12 (1:1) medium (Sigma, United States) supplemented with 20 % fetal bovine serum (HyClone, United States). Colchicine (Sigma, United States) was added 4 h before chromosome harvesting, and the samples were processed by standard techniques. All specimens were G-banded with trypsin-Giemsa (Sigma, United States) to identify chromosomes.

For conventional comparative genomic hybridization (cCGH), test and reference DNA were labeled by nick translation (Rooney, Czepulkowski, 1992). Hybridization of the DNA libraries on metaphase plates derived from peripheral blood lymphocytes of a healthy male was carried out with suppression with 50-fold excess C_0t-1 DNA (Agilent Technologies, United States) for 72 h at 37 °C in a Thermo-Brite hybridization chamber (Abbott Molecular, United States). Metaphase chromosomes were stained with DAPI. Hybridization signals were detected using Axio Imager Z2 fluorescence microscope (Carl Zeiss, Germany) with a set of corresponding filters. The cCGH results were processed with Isis CGH software (Metasystems, Germany).

A search for homozygous regions was performed with SurePrint G3 Human CGH + SNP 4 × 180K microarrays (Agilent Technologies) in the extraembryonic tissues from 22 paired spontaneous abortions with the normal karyotype from 11 women with RPL. Results were visualized with Cytogenomics software (Agilent Technologies). Default Analysis Method (CGH+SNP v2) was used with a LOH threshold of 6.0. The resolution of this platform for LOH detection is about 2 Mb.

Some recurrent homozygous regions were verified by Sanger sequencing. To confirm the status of heterozygosity, 18 single nucleotide polymorphism (SNP) markers located in the analyzed chromosomal regions were chosen. Criteria for the choice of markers: the level of heterozygosity in Caucasians close to 0.5 and uniform distribution within assumed homozygosity regions. DNA sequences flanking the analyzed SNPs (155 to 350 bp for different markers) were analyzed for each marker. In the presence of other polymorphic variants in the analyzed fragments, their heterozygosity status was also taken into account. Sequencing was performed on an Applied Biosystems 3730 automated analyzer with the BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, United States) according to the manufacturer's protocol. Data analysis was performed with Sequencing Analysis v5.4 software.

The analysis of the gene composition was carried out with the "WEB-based GEne SeT AnaLysis Toolkit" program based on overrepresentation enrichment analysis (ORA) (http://www.webgestalt.org). Gene categories were classified ac-

Table 1. List of ROHs

Family	Abortions	Coordinates, GRCh37/hg19	Chromosomal regions	Size, Kb	Total length, Kb	# SNP Probes	# Genes	Heterozygous SNP
1	1a	–	–	–	–	–	–	–
	1b	chr10:59128631-61154870	10q21.1	2026	7993	44	8	0
		chr18:29703102-35670326	18q12.1-q12.2	5967		95	28	7
2	2a	chr5:31798252-34639248	5p13.3-p13.2	2841	16003	50	15	0
		chr7:123895098-127020636	7q31.33	3126		79	6	1
		chr8:50166541-52720312	8q11.21-q11.23	2554		73	2	1
		chr12:39044654-41735719	12q12	2691		56	8	0
		chr14:41387006-46177851	14q21.1-q21.2	4791		73	10	1
	2b	chr7:114786932-120722820	7q31.2-q31.31	5936	11849	75	21	2
		chr17:57263-393-63176847	17q22-q24.1	5913		53	79	0
3	3a	chr1:222474942-228854703	1q41-q42.13	6380	14534	63	65	0
		chr7:85117732-90826127	7q21.11-q21.13	5708		104	23	3
		chr10:57626235-60072490	10q21.1	2446		59	4	0
	3b	chr1:69035118-74558526	1p31.2-p31.1	5523	17172	83	12	3
		chr1:222474942-228854703	1q41-q42.13	6380		65	65	1
		chr7:86143354-90826127	7q21.11-q21.13	4683		88	23	3
		chr10:19811839-25672136	10p12.31-p12.1	5860		94	29	3
4	4a	–	–	–	–	–	–	–
	4b	chr2:153190223-160121961	2q23.3-q24.2	6932	60758	95	19	2
		chr3:175630053-181557730	3q26.31-q26.33	5928		103	20	1
		chr4:38169660-47837883	4p14-p12	9668		146	48	1
		chr4:68962758-77834868	4q13.2-q21.1	8872		108	90	2
		chr9:123453281-132044983	9q33.2-q34.11	8592		81	140	3
		chr11:37140377-39818049	11p12	2678		61	0	0
		chr11:11982521-17593273	11p15.3-p15.1	5611		88	29	1
		chr14:88986214-92648712	14q31.3-q32.12	3662		62	29	1
		chr22:37357169-46172372	22q12.3-q13.31	8815		81	164	0
5	5a	chr11:37902019-40336165	11p12	2434	7327	53	1	0
		chr18:29334151-34227604	18q12.1-q12.2	4893		90	27	4
	5b	–	–	–	–	–	–	–
6	6a	chr3:67122886-70783491	3p14.1-p13	3661	6862	58	12	4
		chr18:32132169-35332795	18q12.1-q12.2	3201		49	20	6
	6b	chr6:80423690-82979725	6q14.1	2556	2556	54	6	0
7	7a	–	–	–	–	–	–	–
	7b	chr14:38541336-41364951	14q21.1	2824	2824	52	9	0
8	8a	–	–	–	–	–	–	–
	8b	chr2:180975918-184732178	2q31.3-q32.1	3756	3756	70	12	2
9	9a	chr6:144072401-147738560	6q24.2-24.3	3666	3666	66	17	1
	9b	chr6:83789798-86115244	6q14.1-q14.3	2325	2325	46	11	2
10	10a	chr2:199760671-205164757	2q33.1-q33.3	5404	13103	87	48	4
		chr11:37115764-39546879	11p12	2431		46	0	0
		chr21:28139416-33407446	21q21.3-q22.11	5268		89	56	4
	10b	chr2:82226742-85375676	2p12-p11.2	3149	5580	49	9	0
		chr11:37115764-39546879	11p12	2431		48	0	0
11	11a	–	–	–	–	–	–	–
	11b	–	–	–	–	–	–	–

cording to "Gene Ontology (GO)" database (http://www.geneontology.org).

Results and discussion

Thirty-nine homozygous regions were identified in extraembryonic tissues of 15 embryos (Table 1). The average size of the identified regions was 4.6 Mb (from 2.0 to 9.6 Mb). Due to the limitation of the resolution of the used platform, adequate comparison of the results with population-specific data available in the literature is difficult. However, comparisons were made with studies in which identified ROHs were ranked by size (McQuillan et al., 2008; Pemberton et al., 2012). It was shown that extended ROHs (>2.5 Mb) are not typical for unrelated individuals and for populations with low levels of inbreeding. (About 20 % of samples had extended ROHs.) In contrast, isolated endogamous populations had a high frequency of extended ROHs (~80 %) (McQuillan et al., 2008). The frequency of extended ROHs in our samples was 68.1 % (15/22). In addition, multiple extended ROHs were detected in 40 % of the samples (9/22). It is possible that the high frequency of extended ROHs is associated with a possible role of inbreeding in the etiology of RPL.

In two embryos from one couple (family # 3), two identical homozygous regions (1q41-q42.13 and 7q21.11-q21.13) and several individual ROHs (3a – 10q21.1, 3b – 1p31.2-p31.1 and 10p12.31-p12.1) were identified. In family # 10, a common ROH (11p12) and additional individual regions (10a – 2q33.1-q33.3 and 21q21.3-q22.11, 10b – 2p12-p11.2) were found. This finding is likely to point to inbreeding, but its verification is impossible at present, as DNA samples from the parents are not available. Several ROHs were detected in more than one embryo but in different families: two ROHs were found in two embryos (7q21.11-q21.13, 10q21.1) and one in three embryos (18q12.1-q12.2).

When comparing the repeated homozygous regions found in this study with the most frequent ROHs in other populations, no matches were found (Nothnagel et al., 2010; Pemberton et al., 2012). This may be indicative of a specific prevalence pattern of ROHs in the Siberian population or result from a strong sample bias in comparison with general populations. For more detailed analysis, characterization of Russian populations by ROH structure, location and frequency of occurrence is required.

Samples with recurrent ROHs were selected for verification by Sanger sequencing (Table 2). As a result, occasional heterozygous SNPs were identified in some regions. Detailed analysis of the results of the microarray study also revealed occasional heterozygous SNPs within the homozygous regions. Out of 39 regions of homozygosity, occasional heterozygous SNPs were present in 25 cases (64 %), whereas only homozygous SNPs were identified in 14 spontaneous abortions (36 %). The presence of heterozygous sites in extended homozygous regions suggests that these chromosome regions are not the result of *de novo* loss of heterozygosity. Such homozygous regions may occur when identical haplotypes are inherited from each parent (Peripolli et al., 2017). Mutations may accumulate in them in a series of generations, leading to heterozygosity in some sites of initially homozygous regions.

The information on clinical effects of ROHs or their associations with phenotypic traits is scarce. One of the possible

Table 2. Genotypes for highly polymorphic SNPs in recurrent ROHs analyzed by Sanger sequencing

Family	Embryo	Coordinates, GRCh37/hg19	Chromosomal regions	Size, Kb	SNP	Genotype
3	3a	chr14:41387006-46177851	14q21.1-q21.2	4791	rs10144740	A
					rs7154765	T
					rs961720	T
4	4a	chr1:222474942-228854703	1q41-q42.13	638	rs2003114	A
	4a	chr7:85117732-90826127	7q21.11-q21.13	5708	rs2519713	T
	4b	chr1:222474942-228854703	1q41-q42.13	638	rs3856155	T
					rs849904	G
	4b	chr7:86143354-90826127	7q21.11-q21.13	4683	rs17301014	A
					rs10281928	AG
					rs4728956	A
5	5b	chr11:37140377-39818049	11p12	2678	rs7942537	C
					rs10768276	A
6	6a	chr11:37902019-40336165	11p12	2434	rs10837260	C
					rs11035463	AG
8	8b	chr14:38541336-41364951	14q21.1	2824	rs2250334	GA
					rs956109	G
					rs9989165	C
					rs7154829	G

mechanisms of the influence of ROH on the pathogenesis of RPL may be homozygotization of recessive mutations significant for early embryo development. Some studies demonstrate that ROHs are significantly associated with many common diseases, such as Alzheimer's disease, rheumatoid arthritis, autism, and coronary artery disease (Yang et al., 2012; Gamsiz et al., 2013; Christofidou et al., 2015; Ghani et al., 2015). Most of the ROHs in our study contained genes; the average number of genes per ROH was about 30. The region 22q12.3-q13.31 of 8 Mb in size contained the largest number of genes, 164 (sample 4b). There were no genes in three spontaneous abortions with corresponding homozygous regions (samples 4b, 10a, and 10b), no known genes were identified. All regions in these samples were mapped to 11p12.

To study the overrepresentation of groups of genes by biological functions among all genes localized in ROHs, enrichment analysis was carried out. As a result, a group of genes involved in the metabolism of flavonoids was identified (GO: 0009812, FDR = 0.0001). This functional group includes mainly genes from the UDP-glucuronosyltransferase family (*UGT2B11*, *UGT2A1*, *UGT2B28*, *UGT2B4*, *UGT2B7*, *UGT2B10*, *UGT2B15*, *UGT2B17*, *UGT2A3*, *SULT1B1*). However, a more detailed analysis showed that all genes from this group mapped to the same region 4q13.2-q21.1 in only one sample, 4b. Consequently, the overrepresentation of this group of genes is due to their nonrandom occurrence within one ROH region but not systemic overrepresentation in different samples. The absence of common pathogenetic pathways for different samples may be indicative of the role of homozygosity for different genes, which is quite possible in the light of the extended size of ROHs and the number of affected genes.

As mentioned above, in addition to regions with occasional heterozygous SNPs, regions containing only homozygous SNPs were identified. Perhaps such sites arise from *de novo* mitotic recombination, that is, UPD occurs. Papenhausen et al. (2011) showed that about 31 % of the samples (29/92) with homozygous regions had appeared from UPD. In our study, 36 % of regions (14/39) without heterozygous SNPs were identified, and they might have been generated by *de novo* mitotic recombination. Imprinting abnormalities can be one of the mechanisms by which such UPD regions contribute to the etiology of miscarriage. When analyzing the gene composition according to the Geneimprint database, five predicted imprinted genes were found: *OBSCN*, *HIST3H2BB*, *LMX1B*, *CELF4*, and *FAM59A*.

Conclusion

This is the first study to demonstrate a high frequency of extended ROHs in spontaneous abortions with a normal karyotype from families with RPL. Future studies should be dedicated to further analysis of the prevalence of ROHs in Russian populations and consideration of this phenomenon from the viewpoint of association with common diseases.

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