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Original Article

Identification of new susceptible genes associated with familial carotid body tumor of Chinese pedigree by high-throughput genome sequencing

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Abstract: Hereditary carotid body tumoris a rare disease which is related to the gene mutation. A majority of tumors are inherited in an autosomal dominant pattern. In addition, high-throughput DNA-sequencing technologies are widely applied to detect disease-associated genes. The Chinese pedigree is examined in this study by using high-throughput genome sequencing and gene mutations were confirmed by peripheral blood of the patients. We finally discovered new 57 genes with SNP and 9 genes with InDel in all patients. Based on the hazardous filter of the results, we found the M1I mutation of the exon1 in the succinate dehydrogenase D (SDHD) gene in all subjects.The new susceptible genesmight regulate the development of carotid body tumor and the result suggests SDHD M1I mutation might play a founder mutation in the Chinese HNPGL patients.

Keywords: Carotid body tumor, whole exome sequencing, gene mutation, founder effect

Introduction

Carotid body tumor (CBT) is extremely rare, agnogenic lesion derived from the parasympathetic and sympathetic nervous systems. The tumor is generally asymptomatic, slow growing and benign, but less than 10% of CBT is malignant [1]. It always arises at the bifurcation of the internal and external carotid arteries and makes up about 65% of head and neck paraganglioma (HNPGL) [2, 3]. Although the majority of HNPGL is reported to be sporadic, approximately 30% HNPGL have the familial characteristic or present as bilateral or multiple primary tumors [4]. It is thought that the sporadic HNPGL is usually induced by hypoxia, but the familial HNPGL could be inclined to relate to genetic mutations such as the exons of the succinate dehydrogenase (SDH) subunits (SDHA, SDHB, SDHC, and SDHD), SDH assembly factor 2 (SDHAF2), VHL, MAX, RET and TMEM127 [5]. Most familial and sporadic HNPGL patients were detected as a result of SDH mutations in the germ-line [6], especially in the SDHD gene [7]. These cases were widely reported in the entire SDHD gene, but they had no obvious hot spots, except for several explicit founder mutations, which could explain the phenomenon of aggregation of familial HNPGL in certain countries [7, 8].

In our present study, we identified a number of new susceptible genes by high-throughput whole exome sequencing, which might be associated with familial CBT. Moreover, we specially analyzed the SDHD gene and compared with previously cases of Chinese familial CBT, and then we found the M1I mutation of the SDHD gene. The M1I mutation is identified as a founder mutation in the Chinese CBT population again [8-11].

Material and methods

Patient and family members

The Pedigree is consisted of four members in this study. A 29-year-old female sought for treatment in our hospital due to painless mass in the bilateral neck, and then the mass was diagnosed as carotid body tumor by digital subtraction angiography (DSA) and histopathologi-

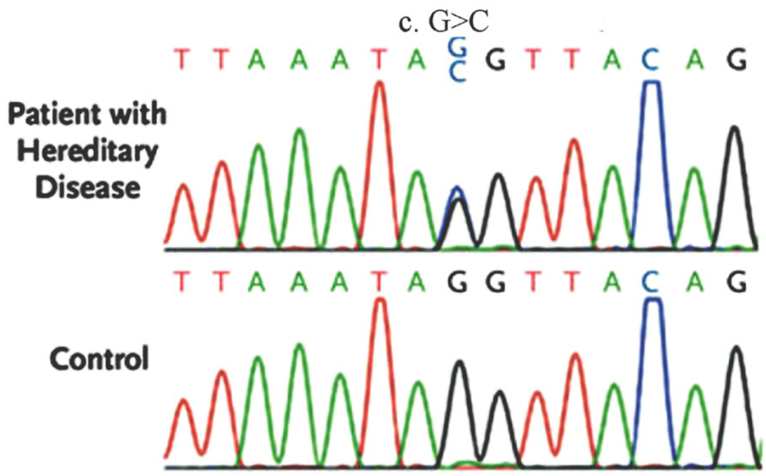

Figure 1. Sequence chromatogram shows the SDHD mutation in the proband. The single base G-to-C substitution in exon 1 results in replacement of the start codon, methionine by isoleuci.

cal examination. A brother of the patient also complained of painless mass of the bilateral neck, which was also confirmed as carotid body tumor, however her father and another brother have unaffected clinically. Ethical approval for this study was given by the Ethical Committee of Peking University Shenzhen Hospital and informed consent was obtained from the participants prior to obtaining their blood samples for the genetic analysis.

Gene sequencing

Sample detection: DNA of the patient and family were extracted from peripheral blood using standard methodology. The purity of DNA samples were quality checked on DNA NanoDrop 1000, the concentration of every sample subsequently was quantified with the Qubit2.0 fluorometer (Life Technologies, UK). Finally, it was used to establish a library that DNA, whose absorbance ratio is range from 1.8 to 2.0, is more than 1.0 μg.

Exome sequencing

Genomic DNA sample was randomly break into fragments with a peak of 180 to 280 bp by using a Covaris S2 sonicator (Covaris, MA, USA), then we repaired bunt-ended fragments with 5' phosphorylated ends and added Klenow and dATP to from the 3'dA overhang. The adaptor-modified ends were screen out through ligate indexing-specific adapters, and then the unligated adaptors were removed by the AMPure XP bead purification. Finally we checked the library by using PCR with SureSelect Primer and SureSelect Pre-capture Reverse PCR primers. If it were up to the standard, we start to sequencing. The exons were captured by using the Agilent SureSelect V6 exome capture platform according to the standard protocol and the whole exome sequencing was performed on the Illumina HiSeq2000 platform. Effective sequencing reads were aligned to the hg19 reference genome using BWA-men (exome-seq). The initial alignment results of BAM format were acquired, then realignment was performed using SAM tools and duplicate reads were removed using Picard. Single-nucleotide Polymorphisms (SNP) and insertion and deletion (InDel) were identified using SAM tools. Sequence variants were annotated by ANNOVAR tool.

Result

Among the two patients in the family with a familial CBT, the whole exome sequencing was performed in four members to identify gene mutations of CBT. Based on the analysis of pattern of autosomal dominant inheritance, we detect 57 candidate genes with SNP and 9 candidate genes with InDel in the patients. Based on the results of the hazardous filter, we found the SDHD gene mutation. The mutation was M1I, located in SDHD-exon 1 (**Figure 1**). Such a mutation changes the nucleotide encoding methionine to isoleucine. The patient's father and brother shared the same mutation with them. We present the three-generation pedigree of the proband (**Figure 2**).

Discussion

More than one-third of PGLs have several susceptibility genes. These genes have some pathogenic mutations, so genetic testing is recommended for all at-risk individuals [12]. In all, 16 different PGL-related genes have been identified by taking the gene isoform analyzed, but it is a laborious and costly process. In recent years, high-throughput DNA-sequencing tech-

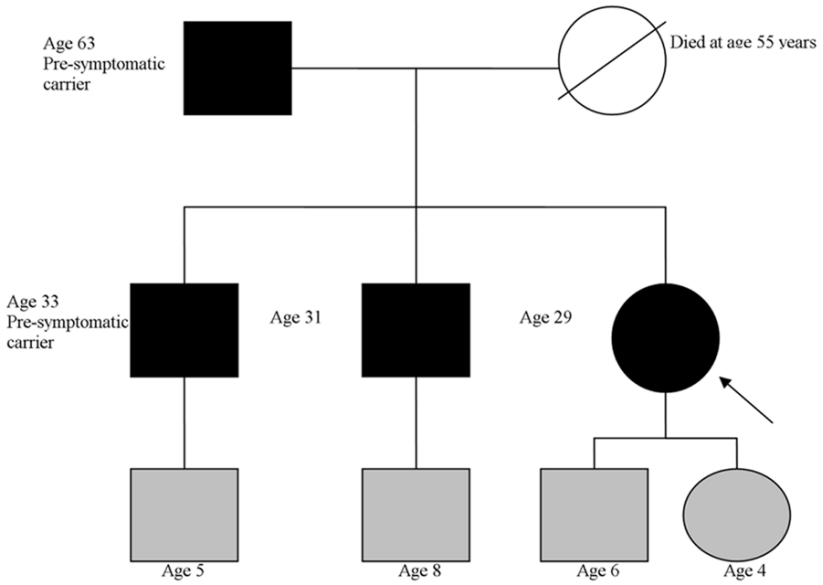

Figure 2. Structure of the pedigree used in the study. Three-generation pedigree including eight members is presented. The arrow designates the proband. Black circles/squares-individuals tested positive for SDHD mutation. Grey circles/squares-individuals not had genetic testing. Current age (years) of individual is displayed next to/below the symbol.

nologies have revolutionized the detection of disease-associated genes based on massively parallel sequencing [13]. In particular, whole exome sequencing (WES), in which the entire coding portion of the gene is targeted and where most disease-associated mutations lie, play a major role in the NGS. With the steady decline in costs, WES gradually replace conventional methods for diagnostics in many genetic disorders [14], including inherited cancers [15]. Notably, four of the PGL-related genes were discovered through WES [12]. The inheritance pattern of Familial HNPGL is considered as autosomal dominant inheritance [7], so we analyzed this pedigree by taking the pattern. We discovered 57 genes with SNP and 9 genes with InDel in all patients subsequently and listed these genes in the Supplementary Table 1. We detected the TMEM25 is one of them and know TMEM127 would cause the HNPGL [5]. TMEM127 is a kind of transmembrane-encoding gene. It could cause PGL with an aberrant mTOR pathway and shed light on cell growth-related signals, if it is disrupted [16]. TMEM25 is initially identified in neoplasm and characterized as a member of the immunoglobulin superfamily, which is associated with immune response, growth factor signal and cell adhesion [17]. It is encoding transmembrane-type as well as TMEM127, so we considered these vicissitudinous genes might regulate the CBT. As is reported, being correlated with SDHD gene mutation, the disease would be influenced with parent of origin effects [7]. In a word, the causative gene is carried and transmitted by parents, but the disease only manifest when the causative gene came from paternal transmission. In our study, all members suffer from SDH deficiency due to M1I mutation of the SDHD gene. The phenomenon hadbeen previously reported and causes a G-to-C substitution in exon 1 of the SDHD gene, resulting in abolishment of the initiation codon [8-11].

A summary of the clinical and genetic features of the four previously reports with Chinese familial HNPGL and our case were presented in the **Table 1**. With regard to the gender of the patients, theSDHD M1I mutation occurs to sixteen men and two women. Seven patients underwent surgery for the treatment and only two patients accepted the radiotherapy. As we know, these Chinese families dispersed in the different areas of the world, with same SDHD gene mutation. The phenomenon is intriguing and significant. We represent the sixth Chinese family carrying this mutation and the fact is consistent with the viewpoint that the SDHD M1I mutation is a founder mutation in the Chinese population [11]. The phenomenon has been noted elsewhere. As is reported, the founder mutations are related to nearly all the familial and sporadic PGL patients in some countries of Europe and North America, but the founder effect cannot play a significant role in other race [11, 18]. Therefore, it is very significant to find a founder mutation, because we can predict the at-risk members by taking genetic sequence strategy, and then we can identify diagnosis when the disease is in a pre-

Table 1. Clinical and genetic character of people with genetic mutations

	Patient/Carrier	Sex	Mutation	Location	Treatment
Familial Australia	1	Male	SDHD M1I	Unknown	Surgery
	2	Male	SDHD M1I	Unknown	Surgery
	3	Male	SDHD M1I	Unknown	Surgery
Familial Singapore	4	Male	SDHD M1I	Bilateral head and neck paragangliomas	Radiotherapy
	5	Male	SDHD M1I	Left-sided carotid body tumor	Radiotherapy
Familial Hong Kong	7	Male	SDHD M1I	Bilateral adrenal phaeochromocytoma	Surgery
	8	Male	SDHD M1I	Bilateral carotid body tumor	Surgery
	9	Male	SDHD M1I	No symptom	No
Familial China 1	10	Male	SDHD M1I	A right carotid body tumor and a glomus jugulare tumor.	Unknown
	11	Male	SDHD M1I	A left carotid body tumor	Unknown
	12	Male	SDHD M1I	No symptom	No
Familial China 2	13	Male	SDHD M1I	Bilateral carotid body tumor	Unknown
	14	Female	SDHD M1I	Aright carotid body tumor	Unknown
Present Family	15	Male	SDHD M1I	No symptom	No
	16	Male	SDHD M1I	No symptom	No
	17	Male	SDHD M1I	Bilateral carotid body tumor	Surgery
	18	Female	SDHD M1I	Bilateral carotid body tumor	Surgery

symptomatic condition and manage at-risk members subsequently. In addition, we discovered a disturbing phenomenon about genotype-phenotype associations of this Pedigree. All healthy phenotype members also carried the mutation. According to the phenomenon, we speculated the father should be a carrier and all patients should have inherited the mutation from their father. Moreover, we have some hypothesis about the healthy phenotype brother. Firstly, the causative gene of this brother might come from his dead mother, so the brother might be just a carrier. Secondly, we know the impact of environment is well obvious to the development of neoplasm. The HNPGL is closely associated with chronic hypoxic stimulation [2, 19], so we suspected the phenotype of this pedigree could be jointly regulated by the environment and hereditary factor. Thirdly, we understand the average (SD) age of patients with familial HNPGL was 38.3 (14.3) years, but the mean age was 47.7 (16.7) years in sporadic HNPGL [20]. Familial HNPGL patients were younger than those with sporadic tumors. We know the brother of normal phenotype is 33 years old, so we speculated he just hasn't reached to the onset of age. Finally and most important, we detected 57 SNP and 9 InDel positions in the patients, so we speculated these vicissitudinous genes might regulate the SDHD gene to express, but regulatory mechanisms remain unclear.

Conclusion

Our current study presents results of high-throughput whole exome sequencing of a Chinese pedigree with HNPGL. We discovered some new susceptible genes, which never be reported. Among them, we find the TMEM25 belongs to the same family as TMEM127, so it could play an important role in the CBT. We believe the risk and function of these new susceptible genes could be found by further research. In addition, we reported the sixth Chinese pedigree with HNPGL, which is regulated by the SDHD M1I mutation. It is the first founder mutation for HNPGL patients confirmed in China. The founder mutation is unique to specific ethnic populations, so it would be substantial important when formulating genetic testing strategies.

Acknowledgements

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Disclosure of conflict of interest

None.

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Supplementary Table 1. The new susceptible genes in patients based on autosomal dominant pattern

Type	ID	GeneName	REF	ALT	Gene	ExonicFunc	cytoBand
SNP	rs12036186	SDF4	G	C	NM_016176	missense SNV	1p36.33
	rs117346635	CFAP74	C	T	NM_001304360	missense SNV	1p36.33
	rs201836187	MORN1	A	G	NM_024848	missense SNV	1p36.33
		NMNAT1	G	C	NM_001297778 NM_001297779 NM_022787	missense SNV	1p36.22
	rs199845652	TTC4	A	G	NM_001291333 NM_004623	missense SNV	1p32.3
		SGIP1	C	T	NM_001308203 NM_032291	missense SNV	1p31.3
	rs139013364	IGSF3	G	A	NM_001007237 NM_001542	stopgain	1p13.1
	rs1142502	NBPF9, NBPF14	C	T	NM_001277444 NM_015383	missense SNV	1q21.2
	rs114846212	CRB1	G	A	NM_001257965 NM_001257966 NM_201253	missense SNV	1q31.3
	rs550293482	RSAD2	G	A	NM_080657	missense SNV	2p25.2
	rs199882056	WDR35	A	G	NM_001006657 NM_020779	missense SNV	2p24.1
	rs192453952	XDH	C	T	NM_000379	missense SNV	2p23.1
	rs56121945	ANKRD36C	G	A	NM_001310154	stopgain	2q11.1
	rs147684628	ANAPC1	C	T	NM_022662	missense SNV	2q13
	rs2304705	KYNU	G	A	NM_001032998 NM_001199241 NM_003937	missense SNV	2q22.2
	rs117569106	BAZ2B	T	A	NM_001289975 NM_013450	missense SNV	2q24.2
	rs2268891	DPP4	A	G	NM_001935	.	2q24.2
	rs200075965	MYO3B	T	C	NM_001083615 NM_138995	missense SNV	2q31.1
	rs146330323	RAPGEF4	T	C	NM_001100397 NM_001282899 NM_001282900 NM_001282901 NM_007023	missense SNV	2q31.1
	rs146196986	AAMP	G	A	NM_001087 NM_001302545	missense SNV	2q35
		PRSS56	C	T	NM_001195129	missense SNV	2q37.1
	rs200423585	USP40	G	A	NM_018218		2q37.1
	rs200244570	DNAJC13	G	A	NM_015268	missense SNV	3q22.1
	rs575644987	TBC1D1	C	T	NM_001253912 NM_001253913 NM_001253914 NM_001253915 NM_015173	missense SNV	4p14
	rs2303654	LHFPL2	T	C	NM_005779	missense SNV	5q14.1
	rs141830505	CMYA5	G	A	NM_153610	missense SNV	5q14.1
	rs142642795	GABRP	G	C	NM_001291985 NM_014211	missense SNV	5q35.1
	rs572301223	COL21A1	C	T	NM_030820	missense SNV	6p12.1

rs147657480	SGK1	T	A	NM_001143676	missense SNV	6q23.2
rs587629467	GTF2IRD2	G	C	NM_173537	missense SNV	7q11.23
rs186514747	RSBN1L	G	A	NM_198467	missense SNV	7q11.23
rs148432464	PCLO	G	A	NM_014510, NM_033026	missense SNV	7q21.11
	ADAM28	A	C	NM_001304351 NM_014265, NM_021777	missense SNV	8p21.2
rs770614747	ZNF33B	T	C	NM_001305033 NM_001305035 NM_001305036 NM_001305037 NM_001305038 NM_001305039 NM_001305040 NM_006955	missense SNV	10q11.21
rs782188288	TMEM25	G	A	NM_001144034 NM_001144035 NM_001144037 NM_001144038 NM_032780	missense SNV	11q23.3
	OR6M1	G	T	NM_001005325	missense SNV	11q24.1
rs55687708	OR8B2	G	A	NM_001005468	missense SNV	11q24.2
rs536588537	ROBO3	T	C	NM_022370	missense SNV	11q24.2
rs573872325	CEP290	T	C	NM_025114	missense SNV	12q21.32
rs201038632	ABCC4	G	C	NM_001301829 NM_005845	missense SNV	13q32.1
rs187901859	TGM1	G	A	NM_000359	missense SNV	14q12
rs192079020	FANCM	G	A	NM_001308133 NM_020937	missense SNV	14q21.2
rs7192962	PDPR	A	T	NM_017990	missense SNV	16q22.1
rs565206764	MYO15A	A	G	NM_016239	missense SNV	17p11.2
rs77630697	SLC47A1	G	A	NM_018242	missense SNV	17p11.2
rs201456656	ME2	C	T	NM_001168335 NM_002396		18q21.2
rs2271260	ATP8B1	C	T	NM_005603	missense SNV	18q21.31
rs141438248	ZNF653	C	T	NM_138783	missense SNV	19p13.2
rs140193183	FARSA	C	A	NM_004461	missense SNV	19p13.2
rs184098931	MVB12A	C	T	NM_001304547 NM_138401	missense SNV	19p13.11
rs200973162	ATF5	G	A	NM_001193646 NM_001290746 NM_012068	missense SNV	19q13.33
rs531836989	SIGLEC11	G	A	NM_001135163 NM_052884	stopgain	19q13.33
rs202027718	VSTM1	C	T	NM_001288791 NM_001288792 NM_001288793 NM_198481		19q13.42
	KIR3DL2	T	A	NM_001242867 NM_006737	missense SNV	19q13.42
	RNF225	C	G	NM_001195135	missense SNV	19q13.43
rs5996646	GSTT2, GSTT2B	G	A	NM_000854, NM_001080843 NM_001302670		22q11.23

	rs143901083	CYLC1	G	T	NM_021118	missense SNV	Xq21.1
	ID	GeneName	REF	ALT	Gene	ExonicFunc	cytoBand
	rs12036186	SDF4	G	C	NM_016176	missense SNV	1p36.33
	rs117346635	CFAP74	C	T	NM_001304360	missense SNV	1p36.33
	rs201836187	MORN1	A	G	NM_024848	missense SNV	1p36.33
		NMNAT1	G	C	NM_001297778 NM_001297779 NM_022787	missense SNV	1p36.22
	rs199845652	TTC4	A	G	NM_001291333 NM_004623	missense SNV	1p32.3
		SGIP1	C	T	NM_001308203 NM_032291	missense SNV	1p31.3
	rs139013364	IGSF3	G	A	NM_001007237 NM_001542	stopgain	1p13.1
InDel	rs761983811	ANKRD36C	TGATAA	T	NM_001310154		2q11.1
	rs200562612	ENPP1	TC	T	NM_006208		6q23.2
	rs369236438	DPP6	TG	T	NM_001039350, NM_001290252, NM_001936, NM_130797		7q36.2
	rs543781934	CPQ	T	TGTTTA	NM_016134	frameshift insertion	8q22.1
		SPATA31E1	ACT	A	NM_178828	frameshift deletion	9q22.1
	rs554677567	CTAGE5	A	ATGTGTGTGTGTG	NM_001247988, NM_001247989, NM_001247990, NM_005930, NM_203354, NM_203355, NM_203356		14q21.1
	rs766696615	GOLGA6L2	ATCT	A	NM_001304388	nonframeshift deletion	15q11.2
	rs530815225	RBBP6	GTA	G	NM_006910, NM_018703		16p12.1
		BPTF	A	AGCCCCCCCC	NM_004459, NM_182641	nonframeshift insertion	17q24.2