(19)中华人民共和国国家知识产权局

(12)发明专利

(10)授权公告号 CN 107475363 B
(45)授权公告日 2021.04.02

(21)申请号 201710496445.7
(22)申请日 2017.06.26
(65)同一申请的已公布的文献号
申请公布号 CN 107475363 A
(43)申请公布日 2017.12.15
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(51)Int.Cl.
C12Q 1/6886(2018.01)
C12Q 1/6809(2018.01)
C12N 15/113(2010.01)

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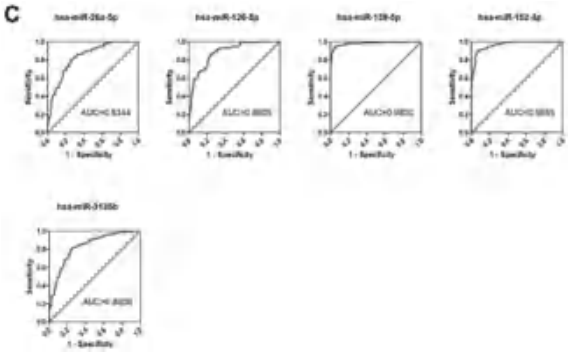
(54)发明名称

一种非小细胞肺癌的生物标记物组合、该生物标记物组合的筛选及其应用

(57)摘要

本发明涉及分子医学诊断领域，具体涉及一种非小细胞肺癌的生物标记物组合、该生物标记物组合的筛选及其应用。所述标记物包括肺腺癌生物标记物和/或鳞状细胞癌生物标记物；所述肺腺癌生物标记物包括hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-152-3p、hsa-miR-451a、hsa-miR-200c-3p、hsa-miR-3135b中的至少一种；所述鳞状细胞癌生物标记物包括hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-151a-3p、hsa-miR-151a-5p、hsa-miR-151b、hsa-miR-152-3p、hsa-miR-550a-3p、hsa-miR-3135b中的至少一种。本发明还提供了上述标记物的筛选方法及其在早期非小细胞肺癌诊断中的应用。本发明实现对非小细胞肺癌进行早期诊断和预测，更快捷、准确，提前了非小细胞肺癌的发现时机，有助于及时尽早的进行治疗，增加存活率。



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1.一种用于检测非小细胞肺癌生物标记物组合的检测试剂,其特征在于,所述生物标记物组合,包括肺腺癌生物标记物和鳞状细胞癌生物标记物;所述肺腺癌生物标记物包括hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-152-3p、hsa-miR-451a、hsa-miR-200c-3p、hsa-miR-3135b;所述鳞状细胞癌生物标记物包括hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-151a-3p、hsa-miR-151a-5p、hsa-miR-151b、hsa-miR-152-3p、hsa-miR-550a-3p、hsa-miR-3135b。

2.根据权利要求1所述的用于检测非小细胞肺癌的生物标记物组合的检测试剂,其特征在于,所述生物标记物组合中hsa-miR-26a-5p,hsa-miR-126-5p,hsa-miR-139-5p,hsa-miR-152-3p和hsa-miR-3135b为肺腺癌和鳞状细胞癌早期筛查的通用生物标记物。

3.根据权利要求1或2所述的检测试剂在制备非小细胞肺癌检测产品中的应用。

4.一种检测非小细胞肺癌的试剂盒,其特征在于,所述试剂盒包含权利要求1或2所述的非小细胞肺癌的生物标记物组合的检测试剂。

5.一种检测非小细胞肺癌的生物芯片,其特征在于,所述生物芯片包含权利要求1或2所述的非小细胞肺癌的生物标记物组合的检测试剂。

一种非小细胞肺癌的生物标记物组合、该生物标记物组合的筛选及其应用

技术领域

[0001] 本发明涉及分子医学诊断领域，具体涉及一种非小细胞肺癌的生物标记物组合、该生物标记物组合的筛选及其应用。

背景技术

[0002] 据世界卫生组织报告，全世界每年有近2000万新发恶性肿瘤患者，约有1100万死于恶性肿瘤。在我国，恶性肿瘤发病与死亡情况更为严峻，《2013年中国肿瘤登记年报》显示，我国每年新发癌症病例约350万，平均每分钟就有6人被诊断为癌症；癌症死亡率为13％，即每7至8人中有1人死亡，年死亡人数达270万例。在众多的恶性肿瘤中，肺癌已成为人体健康头号杀手。在肿瘤治疗方面，各种治疗技术不断更新，新的治疗方法层出不穷，如生物免疫治疗、介入治疗、核医学治疗和分子靶向治疗等。特别是随着在基因水平上对肿瘤发生与发展认识的日益深化，肿瘤医学正在进入一个个性化精确治疗的崭新时代。临床数据显示，如果能在肿瘤发病早期进行有效的治疗和干预，5年生存率至少提高2-3倍。然而，令人触目惊心的是，由于缺乏有效的早期诊断技术，近80％的癌症患者在发现时已经是中晚期，错失最佳治疗时间，所以肿瘤死亡率普遍较高。如何早期发现癌症，已经成为医学界的关注重点。

[0003] 人类基因组通过转录和翻译可表达2万多种蛋白，但参与蛋白质编码的RNA仅占基因组转录产物的2％，其它98％的RNA是不具有编码蛋白功能的非编码RNA(non-coding RNA,ncRNA)。microRNA(miRNA)是近年来研究报道最多的大小约为22个核苷酸的非编码微小RNA。miRNA通过与靶mRNA 3’非翻译区(3’-UTR)结合，使靶mRNA降解或翻译受阻，在转录后水平负调控基因的表达，预计有近一半的人类基因受其调控；功能上涉及一系列生命活动，包括细胞增殖、分化、凋亡、胚胎发育和器官形成等。大量的研究工作已表明，体内miRNA异常与肿瘤的发生和发展密切相关，尤为令人鼓舞的是在血清/血浆中发现了能稳定存在且与人类重大疾病相关的循环miRNA，从而为包括肿瘤在内的各种疾病早期诊断和预后评估开辟了新途径。在肺癌研究方面，Chen等采用RNA测序方法比较健康人血清和NSCLC患者血清中的小分子RNA。结果显示，与正常人血清中的miRNA相比，肺癌患者的血清中有28种miRNA显著下调，63种miRNA显著上调(Chen X,Cell research 2008,18(10):997-1006)。Hu等通过比较60个具有不同生存期的NSCLC病人血清miRNA表达，并在243个病人中进行验证，发现有4种miRNA(miR-486、-1、-30d和-499)与NSCLC病人的生存率关系密切(Hu Z,Journal of clinical oncology,2010,28(10):1721-1726)。Bianchi等针对无症状高危人群，检测血清中34种miRNA的表达谱诊断早期NSCLC的正确率可达80％，灵敏度、特异性分别为71％和90％；Roth等报道，和肺部良性病变相比，肺癌患者血清miR-10b、-141和-155的表达明显增高(Bianchi F,EMBO Mol Med 2011,3(8):495-503)。因此，将循环miRNA的检测应用在肿瘤，尤其是肺癌的早期诊断、预后评估等有着非常重要的科学价值和社会效益。

发明内容

[0004] 鉴于上述现状，本发明提供了一种非小细胞肺癌的生物标记物组合、该生物标记物组合的筛选及其应用，充分利用自主研发的miRNA检测专利技术，旨在鉴别一组非小细胞肺癌早期诊断miRNA生物标记物。

[0005] 为了实现上述发明目的，本发明包含以下技术方案：

[0006] 一种非小细胞肺癌的microRNA生物标记物组合，包括肺腺癌生物标记物和/或鳞状细胞癌生物标记物；所述肺腺癌生物标记物包括hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-152-3p、hsa-miR-451a、hsa-miR-200c-3p、hsa-miR-3135b中的至少一种；所述鳞状细胞癌生物标记物包括hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-151a-3p、hsa-miR-151a-5p、hsa-miR-151b、hsa-miR-152-3p、hsa-miR-550a-3p、hsa-miR-3135b中的至少一种。

[0007] 优选的，所述非小细胞肺癌的microRNA生物标记物组合，包括肺腺癌生物标记物和鳞状细胞癌生物标记物；所述肺腺癌生物标记物包括hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-152-3p、hsa-miR-451a、hsa-miR-200c-3p、hsa-miR-3135b中的至少一种；所述鳞状细胞癌生物标记物包括hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-151a-3p、hsa-miR-151a-5p、hsa-miR-151b、hsa-miR-152-3p、hsa-miR-550a-3p、hsa-miR-3135b中的至少一种。

[0008] 优选的，所述非小细胞肺癌的microRNA生物标记物组合，包括肺腺癌生物标记物和鳞状细胞癌生物标记物；所述肺腺癌生物标记物包括hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-152-3p、hsa-miR-451a、hsa-miR-200c-3p、hsa-miR-3135b；所述鳞状细胞癌生物标记物包括hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-151a-3p、hsa-miR-151a-5p、hsa-miR-151b、hsa-miR-152-3p、hsa-miR-550a-3p、hsa-miR-3135b。

[0009] 优选的，所述非小细胞肺癌的microRNA生物标记物组合，其中hsa-miR-26a-5p，hsa-miR-126-5p，hsa-miR-139-5p，hsa-miR-152-3p和hsa-miR-3135b为肺腺癌和鳞状细胞癌早期筛查的通用生物标记物。

[0010] 一种检测非小细胞肺癌的试剂盒，所述试剂盒包含上述非小细胞肺癌的microRNA生物标记物组合。

[0011] 进一步的，所述生物标记物组合在非小细胞肺癌检测中的应用。

[0012] 一种检测非小细胞肺癌的生物芯片，所述生物芯片包含上述非小细胞肺癌的microRNA生物标记物组合。

[0013] 一种非小细胞肺癌的microRNA生物标记物组合的筛选方法，包括步骤：

[0014] S1、初筛：首先确定候选miRNA范围，然后提取样本的总RNA，采用S-Poly(T)Plus法检测miRNA，筛选出非小细胞肺癌差异性表达的miRNA；

[0015] S2、复筛：对S1中筛选出的非小细胞肺癌差异性表达的miRNA作进一步筛选；

[0016] S3、少量样本单个验证：筛选出潜在的非小细胞肺癌早期诊断生物标记物；

[0017] S4、大量样本单个验证：确定非小细胞肺癌早期诊断生物标记物和通用生物标记物；

[0018] S5、大量新样本单个验证：验证非小细胞肺癌早期诊断生物标记物和通用生物标

记物。

[0019] 进一步的,S1中样本总RNA的提取方法,包括以下步骤:

[0020] (1)向含RNAiso-Plus的离心管中加入样本,吹打混匀,室温静置;加入氯仿,盖紧离心管盖,剧烈振荡,室温静置;

[0021] (2)将(1)所得离心管离心,吸取上清液转移至新的离心管中;

[0022] (3)向(2)所得离心管中加入加入核酸助沉剂,再加入与上清液等体积的异丙醇,充分混匀,-20℃或-80℃静置至少10分钟;

[0023] (4)将(3)所得离心管离心,弃去上清液,向沉淀中加入浓度为75%的乙醇,轻轻颠倒清洗沉淀;离心,完全弃去上清;

[0024] (5)沉淀在室温下干燥,然后加入RNase-free水溶解,所得产物置于-80℃储存,或者直接进行检测。

[0025] 优选地,提取体液中总RNA时,步骤(3)使用糖原(glycogen)作为核酸助沉剂。本发明中将使用糖原作为核酸助沉剂的体液总RNA提取方法命名为S/P miRsol法。

[0026] 进一步优选地,糖原浓度为1.875～120μg/ml。

[0027] 更进一步优选地,糖原浓度为15μg/ml。

[0028] 进一步的,所述样本总RNA提取方法可用于来自细胞或者体液中总RNA提取,所述体液包括血清、血浆、尿液、眼泪、乳汁、唾液、痰液或粪便抽提上清。

[0029] 本发明有益效果:

[0030] 1.本发明提供的非小细胞肺癌的microRNA生物标记物(组合)通过检测体液中的循环miRNA的表达量,即可实现对非小细胞肺癌进行早期诊断和预测,更快捷、准确,提前了非小细胞肺癌的发现时机,有助于及时尽早的进行治疗,增加存活率。

[0031] 2.本发明提供的非小细胞肺癌的microRNA生物标记物(组合)可用于肿瘤预后预测,是一种无创的理想分子标记物,这对肺癌的个性化治疗和提高肺癌的治疗效果将是有重大意义的。

[0032] 3.本发明提供的非小细胞肺癌的microRNA生物标记物(组合)未患肺癌的预测准确率较高,7个microRNA生物标记物联合诊断腺癌个体与正常个体灵敏度可达到89%;9个microRNA生物标记物联合诊断鳞癌个体与正常个体灵敏度可达到97%;5个microRNA通用生物标记物联合诊断非小细胞肺癌与正常个体灵敏度可达到99%。

附图说明

[0033] 图1为非小细胞肺癌循环miRNA生物标记物筛选流程;

[0034] 图2为486个miRNA在非小细胞肺癌(NSCLC)病人血浆中表达谱分析。火山图表示相对于健康组,miRNA在(A)NSCLC stage I和(B)Stage II-IV的表达倍数,数据用fold change(2-Δ ΔCt)展示,用外源掺入的线虫miRNA cel-miR-54做归一化标准;(C)变化倍数显著miRNA统计;(D)125个miRNA在Stage I和Stage II-IV组变化倍数均大于4倍。miRNA的Ct值均小于35,fold change的P value均小于0.05;

[0035] 图3为125个miRNA表达量分层聚类分析。热图绘制了miRNA在健康组(NC)与(A)腺癌Stage I/Stage II-IV;(B)鳞癌Stage I/Stage II-IV表达量之间的关系;

[0036] 图4为30个和38个miRNA表达量分层聚类分析。(A)热图绘制了30个miRNA在健康组

(NC)与腺癌Stage I/Stage II-IV表达量之间的关系;(B)热图绘制了38个miRNA在健康组(NC)与鳞癌Stage I/Stage II-IV表达量之间的关系;

[0037] 图5为miRNA单样本验证预实验。(A)11个miRNA在20个健康志愿者血浆样本与40个腺癌血浆样本中的表达量;(B)10个miRNA在20个健康志愿者血浆样本与20个鳞癌血浆样本中的表达量;其中hsa-miR-32-5p,has-miR-183-5p,hsa-miR-144-5p,has-miR-144-3p和hsa-miR-574-3p(方框标识)在一些样本中Ct值偏大,因此在本轮筛选中予以舍弃;

[0038] 图6为潜在miRNA生物标记物在腺癌/鳞癌所有样本(来源于深圳人民医院)中单个验证。数据为平均值±SE,ns,差异不显著,*<0.05,**<0.01,***<0.001。

[0039] 图7为潜在miRNA生物标记物在腺癌/鳞癌所有样本(来源于广州医科大学肿瘤附属医院)中单个验证。数据为平均值±SE,ns,差异不显著,*<0.05,**<0.01,***<0.001。

[0040] 图8为非小细胞肺癌潜在miRNA生物标记物ROC曲线图。(A)7个腺癌潜在miRNA生物标记物ROC曲线图;(B)9个鳞癌潜在miRNA生物标记物ROC曲线图;(C)5个非小细胞肺癌通用潜在miRNA生物标记物ROC曲线图;

[0041] 图9联合诊断指标ROC曲线图。(A)5个miRNA腺癌生物标记物作为联合诊断指标对腺癌的诊断价值;(B)6个miRNA鳞癌生物标记物作为联合诊断指标对鳞癌的诊断价值;(C)4个miRNA通用内参作为联合诊断指标对非小细胞肺癌的诊断价值。

具体实施方式

[0042] 为了更好的说明本发明,下面结合附图和具体实施方式做进一步说明。如无特别说明,以下实施例中所采用的各种原料均来源于市场销售,所采用的方法均为常规方法,其中引物、探针来自美国Integrated DNATechnologies(IDT)公司。

[0043] 本申请中主要材料来源如下:

[0044] 临床上将肺癌分为非小细胞肺癌(non-small cell lung cancer,NSCLC)和小细胞肺癌(small cell lung cancer,SCLC)两大类。NSCLC主要包括肺腺癌、鳞状细胞癌和大细胞癌,分别占肺癌的40%、25%和10%。为了控制样本间的异质性,本研究只采用腺癌(ADC)和鳞状细胞癌(SCC)两种血浆样本。血浆收集流程如下:

[0045] 用含有EDTA抗凝剂的收集管采集全血,3,000×g,4℃离心10min。转移上清至RNase-free EP管中,储存于-80℃。由于miRNA也存在于红细胞中,为了防止影响检测结果,所有肉眼可见的溶血样本全部被剔除。符合标准的样本共有266份健康血浆和288份非小细胞肺癌患者血浆,收集于深圳人民医院;149例健康血浆,149例非小细胞肺癌血浆收集于广州医科大学肿瘤附属医院。

[0046] 实施例1、初筛非小细胞肺癌差异性表达的miRNA

[0047] 在本实施例中,包含以下步骤:

[0048] (一)本发明的目标为系统地研究循环miRNA与非小细胞肺癌的关系,以期找出一组可作为非小细胞肺癌早期诊断生物标记物的miRNA。首先通过文献检索的方式确定候选研究miRNA范围,搜索关键词为“microRNA/miRNA”和“cancer”。共计486个miRNA被确定为候选研究目标(表1)。

[0049] (二)制备混合样本。所有样本(来自于深圳市人民医院)被分为三组,包括266份健康人血浆,130份非小细胞肺癌I期病人血浆和158份II-IV期病人血浆,分别混合均匀。

[0050] (三)提取血浆总RNA,本实施例中使用S/P miRsol方法提取血浆总RNA,具体步骤为:

[0051] 1)0.1pM线虫miRNA cel-miR-54作为内参提前加入1ml的RNAiso-Plus(TaKaRa)中,加入100uL血清,吹打混匀,室温静置5分钟;加入200μl氯仿,盖紧离心管盖,剧烈振荡20秒;室温静置5分钟;

[0052] 2)12,000g,4℃离心15分钟;小心取出离心管,此时匀浆液分为三层,即:无色的上清液(含miRNA)、中间的白色蛋白层、及有颜色的下层有机相;吸取500μl上清液转移至另一新的1.5ml离心管中;优选地,还包括二次抽提总RNA:向所述移除上清液的离心管中加入与移除上清液等体积的RNase-free水,混匀,12,000g,4℃离心15分钟;吸取500μL上清液到另一个新的离心管。

[0053] 3)向上清液中加入5uL糖原(Applichem),使糖原终浓度为15μg/ml,再加入与上清液等体积的异丙醇(505uL),上下颠倒充分混匀,-20℃或-80℃静置至少10分钟;

[0054] 4)13,500g,4℃离心10分钟;弃去上清液,向沉淀中加入1ml的75%乙醇,轻轻颠倒清洗沉淀;13,500g,4℃离心5分钟,完全弃去上清,如管壁上沾有残余溶液,应再次离心并弃尽上清;

[0055] 5)沉淀室温干燥2～3分钟,加入20μl RNase-free水溶解,溶解产物置于-80℃储存,或者直接进行miRNA的荧光定量PCR检测。用提取的血清总RNA进行miRNA的定量检测。

[0056] (四)S-Poly(T)Plus法检测miRNA,在本实施例中,在每一组的混合血浆样本中分别检测486个与癌症相关的miRNA(表1),具体步骤如下:

[0057] 1)加尾逆转录:miRNA加Poly(A)尾和第一链cDNA的合成在一个反应体系中完成,利用S-Poly(T)引物进行miRNA的逆转录,加尾逆转录的反应体系包含多聚腺苷酸聚合酶(polyA polymerase)和逆转录酶(reverse transcriptase)。

[0058] 加尾逆转录的反应体系包含:5.5μL血清总RNA,1μL的10μM RT primer(逆转录引物),1U的PolyA Polymerase,100U的MMLV(鼠白血病逆转录酶),2.5μL的4×reaction buffer(反应缓冲液),RNase-free Water(无RNA酶水)补足至10μL。所述4×reaction buffer包含200mM Tris-HCl,600mM NaCl,40mM MgCl2,4mM ATP,2mM dNTP,pH 8.0。加尾逆转录的反应条件为:37℃保温30min,42℃保温30min,75℃保温5min,迅速置于冰上,静置2min。

[0059] 所述S-Poly(T)引物由四部分组成,其序列从5'端到3'端依次为:14～20个碱基的PCR通用引物序列、14～20个碱基的通用探针序列、11个oligo(dT)和5～7个与miRNA 3'配对的特异性碱基。检测不同miRNA的S-Poly(T)引物序列如表1所示。

[0060] 2)PCR:以步骤1)中获得的第一链cDNA为模板,用miRNA特异上游引物和下游通用引物进行real-time PCR定量检测。所述miRNA特异上游引物是不含3'端3～8个碱基的miRNA特异序列,所述miRNA的下游通用引物来自于S-Poly(T)引物的14～20个碱基的通用引物序列。

[0061] Real-time PCR定量检测采用探针法或者SYBR荧光染料法。本实施例中采用探针法,所用探针为通用探针,其序列来自于S-Poly(T)引物上14～20个碱基的PCR通用引物序列。

[0062] Real-time PCR的反应体系为:

[0063]

组分	含量
4×qPCR Reaction Buffer(Geneup,μl)	5
1μM Forward Primer(μl)	4
10μM universal reverseprimer(μl)	0.4
10μM universal Taqmanprobe(μl)	0.5
100×ROX Rerference Dye(μl)	0.2
hotstart Taq Polymerase(Geneup,U)	0.5
Diluted cDNA(μl)	0.5
RNase-free Water up to(μl)	20

[0064] PCR运行仪器为ABI StepOnePlus thermal cycler,反应条件为:预变性95℃3分,变性95℃10s,退火60℃30s,40个循环。每个PCR反应三个复孔。本实施例中相对表达量用2-ˆΔCt计算,数据用Spiked-in(cel-miR-54)归一化。数据分析使用GraphPad Prism 5软件,检验方法为two-tailed Student's test。最终结果用平均值±SD(标准差)表示。

[0065] 用S-Ploy(T)Plus的方法在这三组中分别检测486个miRNA,火山图如图2A和图2B。相对于健康组,miRNA在非小细胞肺癌I期组表达量大于2倍和4倍的分别有188个和91个;在II-IV期表达量大于2倍和4倍的分别有187个和102个(图2C);miRNA在I期组表达量大于4倍,并且在II-IV期表达量大于4倍的共有125个(图2D和图3),以上所有miRNA Ct值均小于35,fold change的P value均小于0.05。

[0066] 实施例2、复筛非小细胞肺癌差异性表达的miRNA

[0067] 在第二轮的筛选中,具体实验操作均同实施例1。来自于深圳市人民医院的544例血浆样本被分为五组:NC(N=266),ADC Stage I(N=96),ADC Stage II-IV(N=113),SCC Stage I(N=34)和SCC Stage II-IV(N=45)。分别在五组混合样品中检测实施例1中筛选出来的125个miRNA的表达量。在这轮筛选挑选标准为:Stage I vs.NC:fold-change>2,或者Stage II-IV vs.NC:fold change>2。符合标准的miRNA在腺癌中有30个,在鳞癌中有38个(图4)。

[0068] 实施例3、腺癌/鳞癌miRNA生物标记物单个验证预实验

[0069] 实施例2中筛选出的miRNA首先用少量随机样本(收集于深圳市人民医院)进行单样本验证。挑选的样本数量具体为:健康组(NC)(N=20),腺癌I期(N=20),腺癌II-IV期(N=20),鳞癌I期(N=10)和鳞癌II-IV期(N=10)。在这轮筛选挑选标准为:I期vs.健康组:fold-change>2,或者II-IV期vs.健康组:fold change>2。符合标准的miRNA在腺癌中共有11个,在鳞癌中共有10个(图5)。其中hsa-miR-32-5p,has-miR-183-5p,hsa-miR-144-5p,has-miR-144-3p和hsa-miR-574-3p在一些腺癌和鳞癌样本中Ct值大于35,予以舍弃。因此在本实施例中共筛选出7个miRNA(腺癌)和9个miRNA(鳞癌)作为潜在的非小细胞肺癌早期诊断生物标记物。

[0070] 实施例4、大样本验证7个/9个miRNA在腺癌/鳞癌中的表达量

[0071] 实施例3中筛选出的潜在生物标记物在266例健康血浆,288例非小细胞肺癌血浆样本(收集于深圳人民医院)中进行单样本验证。所用样本数量为健康对照(NC)(N=210),腺癌I期(N=94),腺癌II期(N=17),腺癌III期(N=53),腺癌IV期(N=36),鳞癌I期(N=34),鳞癌II期(N=20),鳞癌III期(N=21),鳞癌IV期(N=4)。目标miRNA在健康组和非小细

胞肺癌组之间的表达量都有显著差异(P<0.001)(图6)。因此在本次发明中,我们共确定7个腺癌早期筛查生物标记物,分别为hsa-miR-26a-5p,hsa-miR-126-5p,hsa-miR-139-5p,hsa-miR-152-3p,hsa-miR-451a,hsa-miR-200c-3p,hsa-miR-3135b;9个鳞癌早期筛查生物标记物,分别为hsa-miR-26a-5p,hsa-miR-126-5p,hsa-miR-139-5p,hsa-miR-151a-3p,hsa-miR-151a-5p,hsa-miR-151b,hsa-miR-152-3p,hsa-miR-550a-3p,hsa-miR-3135b。其中5个miRNA包含hsa-miR-26a-5p,hsa-miR-126-5p,hsa-miR-139-5p,hsa-miR-152-3p和hsa-miR-3135b是腺癌和鳞癌早期筛查通用生物标记物。

[0072] 实施例五新样本验证7个/9个miRNA在腺癌/鳞癌中的表达量

[0073] 149例健康血浆,83例腺癌血浆,66例鳞癌血浆收集于广州医科大学肿瘤附属医院,用于本次验证。所用样本数量具体为Healthy(N=149),ADC Stage I(N=23),ADC Stage II(N=20),ADC Stage III(N=20),ADC Stage IV(N=20),SCC Stage I(N=7),SCC Stage II(N=19),SCC Stage III(N=20),SCC Stage I(N=20)。miRNA在健康组和肺癌组的表达量如图7所示。结果表明,7个/9个miRNA在新样本中的表达形式与上一批样本基本一致,说明筛选出的miRNA作为潜在的生物标记物是稳定可靠的。

[0074] 实施例六miRNA在非小细胞肺癌诊断中的价值

[0075] 为了构建区分肺癌与正常人的miRNA诊断标准,我们评估了7个/9个miRNA在腺癌/鳞癌患者和正常人血浆中的相对表达量。ROC曲线表明目标miRNA作为腺癌/鳞癌生物标记物AUC(曲下面积)分别达到0.75～0.94(图8A),0.80～0.99(图8B)(p value均小于0.001),表明较好的诊断效果。其中5个miRNA为腺癌和鳞癌通用潜在生物标记物,即hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-152-3p和hsa-miR-3135b,通用miRNA生物标记物AUC达到0.83～0.98(图8C)(p value均小于0.001)。

[0076] 实施例七联合诊断的指标的筛选

[0077] 利用Logistic回归分析,hsa-miR-26a-5p、hsa-miR-126-5p、hsa-miR-139-5p、hsa-miR-451a和hsa-miR-3135b被选入腺癌诊断标准,5个miRNA作为联合诊断指标能以AUC 0.89区分腺癌个体和正常个体(图9A)。这5个miRNA联合诊断腺癌为阳性的概率为p,则ln(p/(1-p))=-6.632×(hsa-miR-26a-5p)+36.668×(hsa-miR-126-5p)+78.531×(hsa-miR-139-5p-0.042)×(hsa-miR-451a)-0.272×(hsa-miR-3135b);

[0078] hsa-miR-139-5p,hsa-miR-151a-3p,hsa-miR-151a-5p,hsa-miR-151b,hsa-miR-550a-3p和hsa-miR-3135b被选入鳞癌诊断标准,6个miRNA作为联合诊断指标能以AUC 0.96区分鳞癌个体和正常个体(图9B)。这6个miRNA联合诊断鳞癌为阳性的概率为p,则ln(p/(1-p))=357.275×(hsa-miR-139-5p)+19.103×(hsa-miR-151a-3p)-81.391×(hsa-miR-151a-5p)+132.895×(hsa-miR-151b)-905.226×(hsa-miR-550a-3p)-2.074×(hsa-miR-3135b)-3.29。

[0079] 5个非小细胞肺癌通用生物标记物中有4个miRNA被选入通用诊断标准,即hsa-miR-26a-5p、hsa-miR-139-5p、hsa-miR-152-3p和hsa-miR-3135b,4个miRNA作为联合诊断指标能以AUC 0.99区分非小细胞肺癌个体和正常个体(图9C)。这4个miRNA联合诊断非小细胞肺癌的概率为p,则

[0080] ln(p/(1-p))=-8.775×(hsa-miR-26a-5p)+108.928×(hsa-miR-139-5p)+741.866×(hsa-miR-152-3p)-0.168×(hsa-miR-3135b)-5.714。

[0081] 表1本发明中所检测的miRNA及所使用的引物和探针序列

[0082]

miRNA	sequence (5'-3')	forward primer	RT primer
>hsa-miR-215-5p MIMAT0000272	augaccuaugaauugacagac	tgtcggatgacctatgaattg	gtgcagggtccgaggtcagagccacctgggcaattttttttttgtctgt
>hsa-miR-2355-3p MIMAT0017950	auuguccuugcuguuuggagau	ttcggattgtccttgctgttt	gtgcagggtccgaggtcagagccacctgggcaatttttttttttatctcc
>hsa-miR-3146 MIMAT0015018	caugcuaggauagaaagaaugg	ttcggcatgctaggatagaaa	gtgcagggtccgaggtcagagccacctgggcaatttttttttttccattc
>hsa-miR-29b-3p MIMAT0000100	uagcaccauuugaaaucaguguu	tcggtagcaccatttgaaatc	gtgcagggtccgaggtcagagccaoctgggcaatttttttttaacact
>hsa-miR-153-3p MIMAT0000439	uugcauagucacaaaagugauc	gtcggttgcatagtcacaaaa	gtgcagggtccgaggtcagagccacctgggcaatttttttttgatcac
>hsa-miR-15a-3p MIMAT0004488	caggccauauugugcugccuca	cggcaggccatattgtgct	gtgcagggtccgaggtcagagccacctgggcaatttttttttgaggca
>hsa-miR-1307-5p MIMAT0022727	ucgacccggaccucgaccggcu	tggtcgacccggacctega	gtgcagggtccgaggtcagagccacctgggcaatttttttttttagccgg
>hsa-miR-221-5p MIMAT0004568	accuggcauacaauguagauuu	tcggacctggcatacaatgt	gtgcagggtccgaggtcagagccacctgggcaatttttttttttaaatct
>hsa-miR-502-5p MIMAT0002873	auccuugcuaucuggugcua	ttcggatcctgctatctgg	gtgcagggtccgaggtcagagccacctgggcaatttttttttttagcacc
>hsa-let-7b-3p MIMAT0004482	cuauacaaccuacugccuucc	tcggctatacaacctactgc	gtgcagggtccgaggtcagagccacctgggcaatttttttttgggaag
>hsa-miR-199b-5p MIMAT0000263	cccaguguuuagacuaucuguuc	cggcccagtgttagactat	gtgcagggtccgaggtcagagccacctgggcaatttttttttgaacag
>hsa-miR-378h MIMAT0018984	acuggacuuggugucagaugg	tcggactggacttggtgtc	gtgcagggtccgaggtcagagccacctgggcaatttttttttccatct
>hsa-miR-3169 MIMAT0015044	uaggacugugcuuggcacauag	tggtaggactgtgcttggc	gtgcagggtccgaggtcagagccacctgggcaatttttttttttctatgt
>hsa-miR-376b MIMAT0002172	aucauagaggaaaauccauguu	gtcggatcatagaggaaaatc	gtgcagggtccgaggtcagagccacctgggcaatttttttttaacatg
>hsa-miR-1915-3p MIMAT0007892	ccccagggcgacgcggcggg	ggccccagggcgacgc	gtgcagggtccgaggtcagagccacctgggcaatttttttttcccgcc
>hsa-miR-17-3p MIMAT0000071	acugcagugaaggcacuuguag	tggactgcagtgaaggcac	gtgcagggtccgaggtcagagccacctgggcaatttttttttttctacaa
>hsa-miR-199b-3p MIMAT0004563	acaguagucugcacauugguua	tcggacagtagtctgcacat	gtgcagggtccgaggtcagagccacctgggcaatttttttttttaaccaa
>hsa-miR-142-3p MIMAT0000434	uguaguguuuccuacuuuaugga	tcggtgtagtgtttcctactt	gtgcagggtccgaggtcagagccaoctgggcaatttttttttttccataa
>hsa-miR-3653-3p MIMAT0018073	cuaagaaguugacugaag	tcggtcggctaagaagttga	gtgcagggtccgaggtcagagccacctgggcaatttttttttttcttcag
>hsa-miR-3164 MIMAT0015038	ugugacuuuaagggaaauggcg	ttcggtgtgacttaagggaa	gtgcagggtccgaggtcagagccacctgggcaatttttttttttcgccat
>hsa-miR-27b-3p MIMAT0000419	uucacaguggcuaaguucugc	ttcggttcacagtggctaag	gtgcagggtccgaggtcagagccacctgggcaatttttttttttgcagaa
>hsa-miR-223-5p MIMAT0004570	cguguauuugacaagcugaguu	tcggcgtgtatttgacaagc	gtgcagggtccgaggtcagagccaoctgggcaatttttttttttaactca
>hsa-miR-486-3p	cgggggcagcucaguac	tggcgggggcagctcagta	gtgcagggtccgaggtcagagcca

[0083]

MIMAT0004762	aggau		cctgggcaatttttttttttatcctg
>hsa-miR-496 MIMAT0002818	ugaguauuacauggcc aaucuc	tcggtgagtattacatggcc	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttgagatt
>hsa-miR-493-3p MIMAT0003161	ugaaggucuacugugu gccagg	tcggtgaaggtctactgtgt	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttcctggc
>hsa-let-7a-5p MIMAT0000062	ugagguaguagguugu auaguu	tcggtgaggtagtaggttgt	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttaactat
>hsa-miR-361-3p MIMAT0004682	uccccccaggugugauu cugauuu	tgtcccccaggtgtgattc	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttaaatca
>hsa-miR-3148 MIMAT0015021	uggaaaaaacuggugu gugcuu	ttcggtggaaaaaaactggtgt	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttaagcac
>hsa-miR-15b-3p MIMAT0004586	cgaaucauuauuugcu gcucua	gtcggcgaatcattatttgct	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttagagca
>hsa-miR-609 MIMAT0003277	agggugauuucucucau cucu	gtcggagggtgtttctctc	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttagagat
>hsa-miR-584-3p MIMAT0022708	ucaguuccaggccaac caggcu	tggtcagttccaggccaac	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttagcctg
>hsa-miR-154-5p MIMAT0000452	uagguuauccguguug ccuucg	tcggtaggttatccgtgttg	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttcgaagg
>hsa-miR-584-5p MIMAT0003249	uuauggauuuguccuggg acugag	cggttatggtttgcctggg	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttctcagt
>hsa-miR-1226-3p MIMAT0005577	ucaccagcccuguguu ccccuag	tggtcaccagccctgtgtt	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttctaggg
>hsa-miR-519a-5p MIMAT0005452	cucuagagggaagcgc uuucug	ggctctagagggaagcgc	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttcagaaa
>hsa-miR-196b-3p MIMAT0009201	ucgacagcacgacacu gccuuc	tggtcgacagcacgacact	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttgaaggc
>hsa-miR-579 MIMAT0003244	uucauuugguauaaacc cgcgauu	ttcggttcattggtataaacc	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttaatcgc
>hsa-miR-126-3p MIMAT0000445	ucguaccgugaguaau aaugcg	tcggtcgtaccgtgagtaat	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttcgcatt
>hsa-miR-339-3p MIMAT0004702	ugagcgccucgacgac agagccg	gtgagcgcctcgacgaca	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttcggctc
>hsa-miR-185-5p MIMAT0000455	uggagagaaaggcagu uccuga	cggtggagagaaaggcagt	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttcaggaa
>hsa-miR-182-5p MIMAT0000259	uuuggcaaugguagaa cucacacu	tggtttggcaatggtagaact	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttagtgtg
>hsa-miR-30b-5p MIMAT0000420	uguaaacauccuacac ucagcu	ttcggtgtaaacatcctacac	gtgcagggtccgaggtcagagcca cctgggcaatttttttttttagctga
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Universal Taqman probe	56-FAM/CAGAGCCAC/ZEN/CTGGGCAATTT/3IABkFQ		

[0104] 以上所述实施例仅表达了本发明的几种实施方式，其描述较为具体和详细，但并不能因此而理解为对本发明专利范围的限制。应当指出的是，对于本领域的普通技术人员来说，在不脱离本发明构思的前提下，还可以做出若干变形和改进，这些都属于本发明的保护范围。因此，本发明专利的保护范围应以所附权利要求为准。

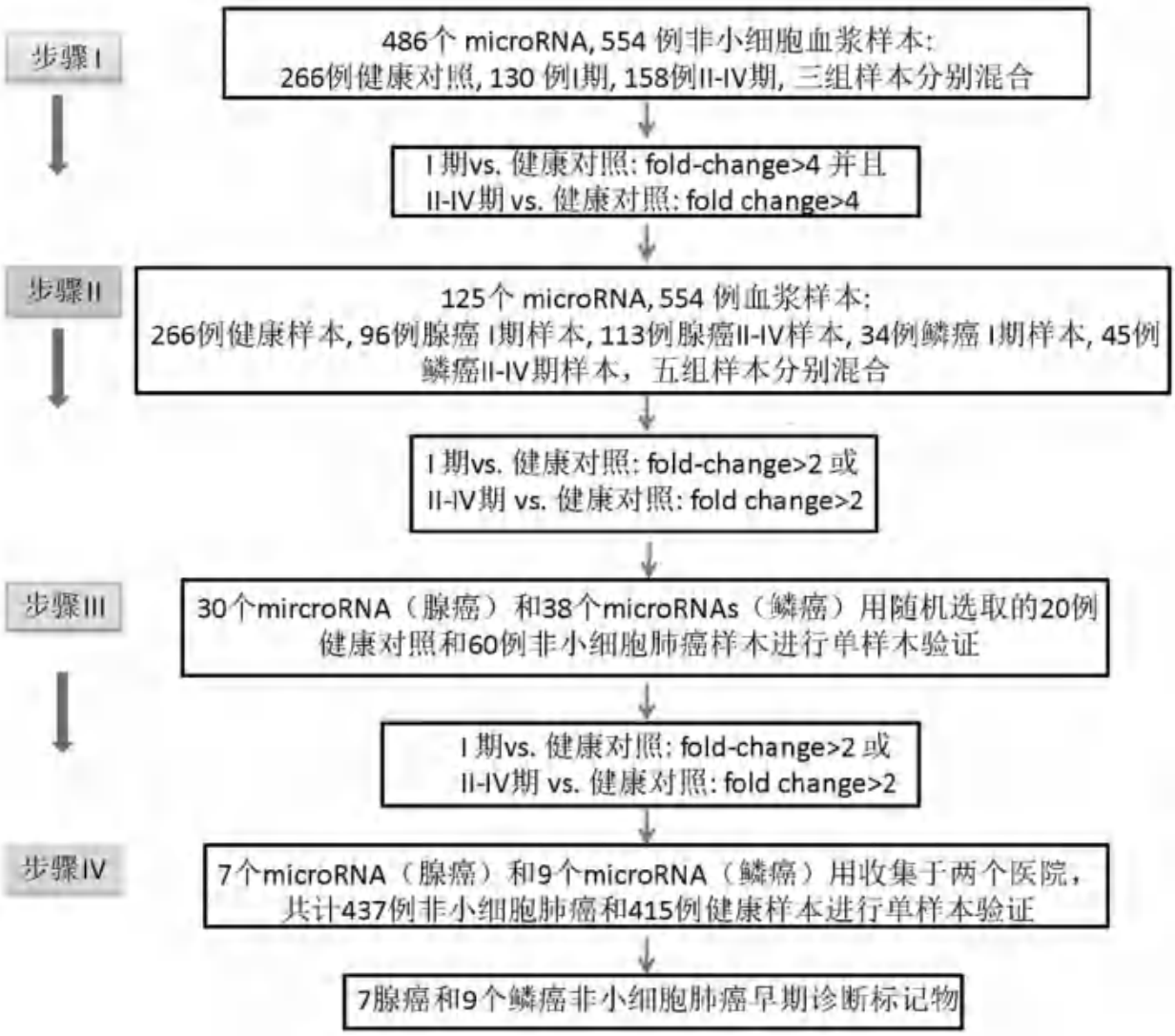
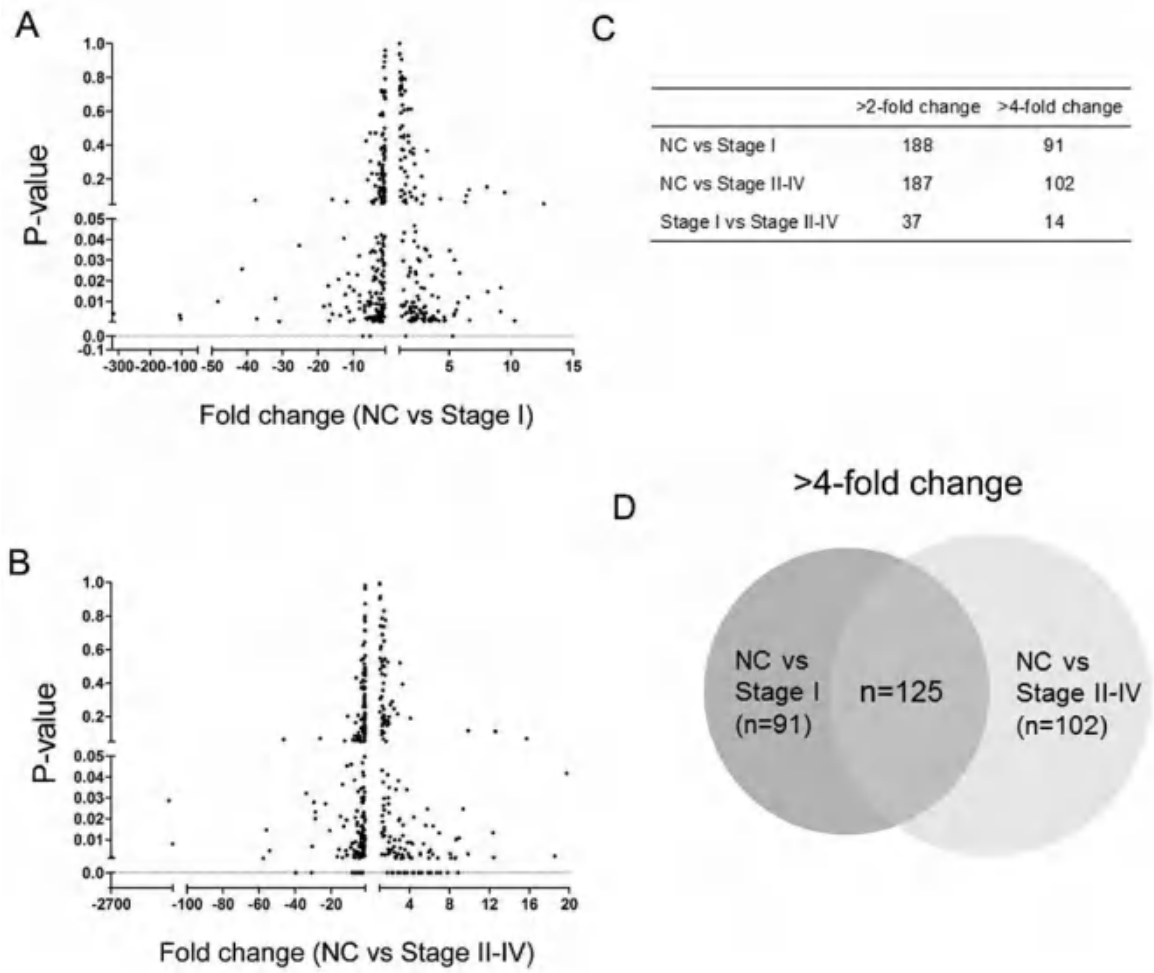

步骤I
486个 microRNA, 554 例非小细胞血浆样本:
266例健康对照, 130 例I期, 158例II-IV期, 三组样本分别混合
I 期vs. 健康对照: fold-change>4 并且
II-IV期 vs. 健康对照: fold change>4
步骤II
125个 microRNA, 554 例血浆样本:
266例健康样本, 96例腺癌 I期样本, 113例腺癌II-IV样本, 34例鳞癌 I期样本, 45例鳞癌II-IV期样本，五组样本分别混合
I 期vs. 健康对照: fold-change>2 或
II-IV期 vs. 健康对照: fold change>2
步骤III
30个mircroRNA（腺癌）和38个microRNAs（鳞癌）用随机选取的20例健康对照和60例非小细胞肺癌样本进行单样本验证
I 期vs. 健康对照: fold-change>2 或
II-IV期 vs. 健康对照: fold change>2
步骤IV
7个microRNA（腺癌）和9个microRNA（鳞癌）用收集于两个医院，共计437例非小细胞肺癌和415例健康样本进行单样本验证
7腺癌和9个鳞癌非小细胞肺癌早期诊断标记物

图1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P-value
Fold change (NC vs Stage I)
B
P-value
Fold change (NC vs Stage II-IV)
C
>2-fold change >4-fold change
NC vs Stage I 188 91
NC vs Stage II-IV 187 102
Stage I vs Stage II-IV 37 14
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n=125
NC vs Stage II-IV (n=102)

图2

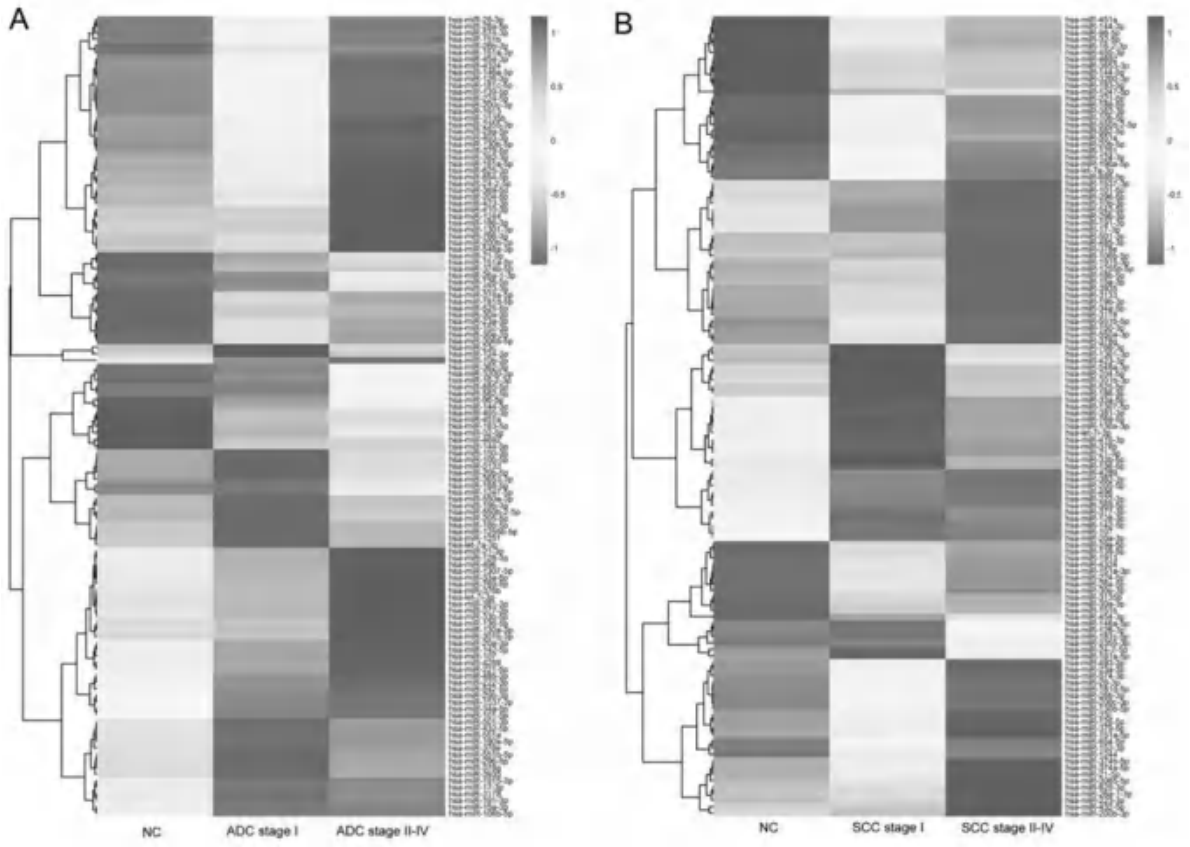
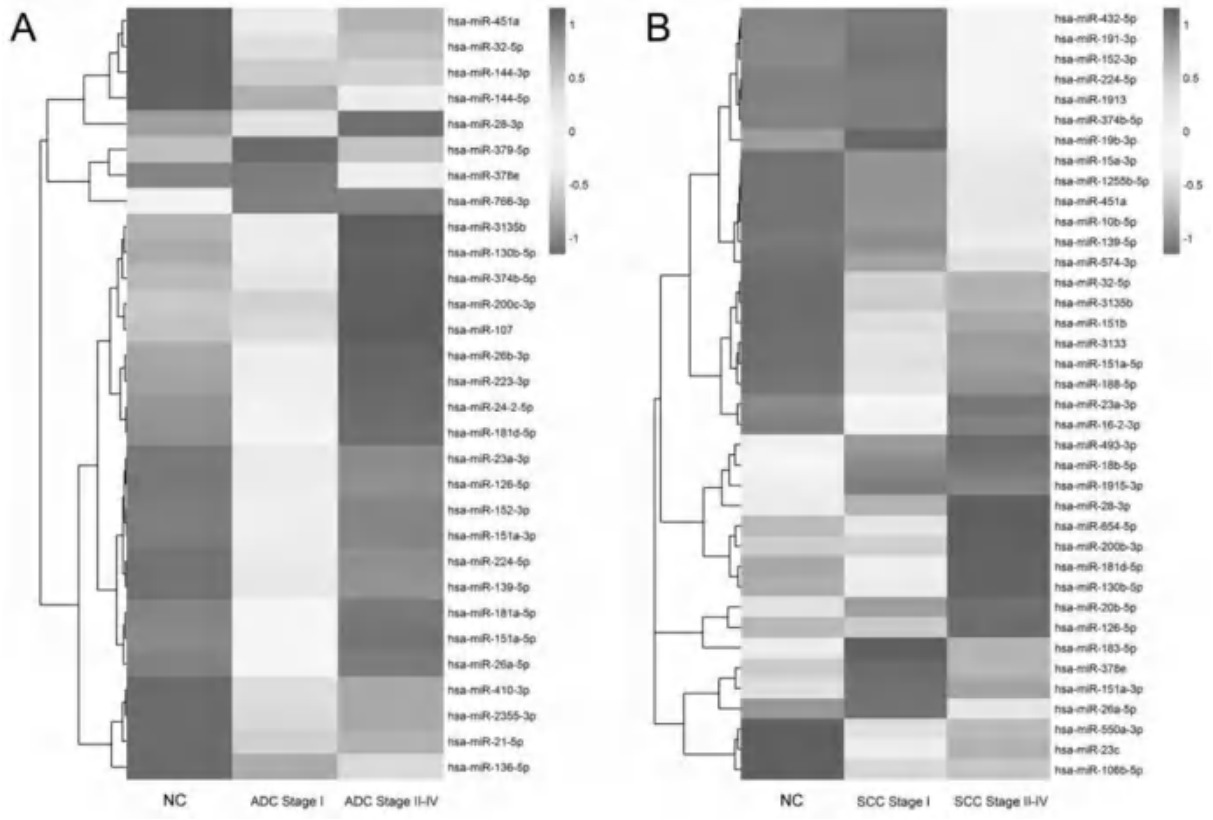


图3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hsa-miR-126-5p
hsa-miR-152-3p
hsa-miR-151a-3p
hsa-miR-224-5p
hsa-miR-139-5p
hsa-miR-181a-5p
hsa-miR-151a-5p
hsa-miR-26a-5p
hsa-miR-410-3p
hsa-miR-2355-3p
hsa-miR-21-5p
hsa-miR-136-5p
1
0.5
0
-0.5
-1
NC
ADC Stage I
ADC Stage II-IV
B
hsa-miR-432-5p
hsa-miR-191-3p
hsa-miR-152-3p
hsa-miR-224-5p
hsa-miR-1913
hsa-miR-374b-5p
hsa-miR-19b-3p
hsa-miR-15a-3p
hsa-miR-1255b-5p
hsa-miR-451a
hsa-miR-10b-5p
hsa-miR-139-5p
hsa-miR-574-3p
hsa-miR-32-5p
hsa-miR-3135b
hsa-miR-151b
hsa-miR-3133
hsa-miR-151a-5p
hsa-miR-188-5p
hsa-miR-23a-3p
hsa-miR-16-2-3p
hsa-miR-493-3p
hsa-miR-18b-5p
hsa-miR-1915-3p
hsa-miR-28-3p
hsa-miR-654-5p
hsa-miR-200b-3p
hsa-miR-181d-5p
hsa-miR-130b-5p
hsa-miR-20b-5p
hsa-miR-126-5p
hsa-miR-183-5p
hsa-miR-378e
hsa-miR-151a-3p
hsa-miR-26a-5p
hsa-miR-550a-3p
hsa-miR-23c
hsa-miR-106b-5p
1
0.5
0
-0.5
-1
NC
SCC Stage I
SCC Stage II-IV

图4

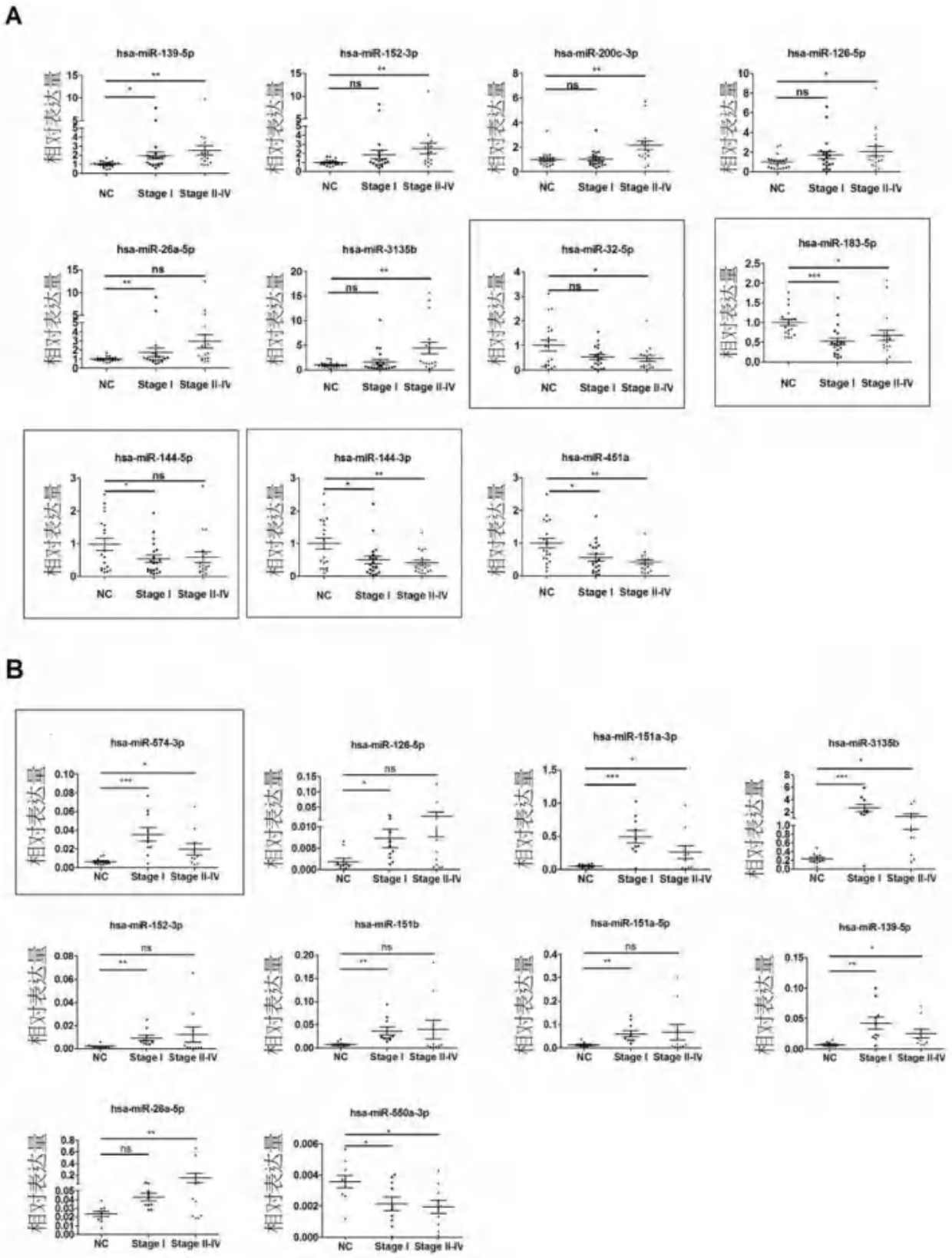

A
hsa-miR-139-5p
hsa-miR-152-3p
hsa-miR-200c-3p
hsa-miR-126-5p
hsa-miR-26a-5p
hsa-miR-3135b
hsa-miR-32-5p
hsa-miR-183-5p
hsa-miR-144-5p
hsa-miR-144-3p
hsa-miR-451a
B
hsa-miR-574-3p
hsa-miR-126-5p
hsa-miR-151a-3p
hsa-miR-3135b
hsa-miR-152-3p
hsa-miR-151b
hsa-miR-151a-5p
hsa-miR-139-5p
hsa-miR-26a-5p
hsa-miR-550a-3p
相对表达量
NC
Stage I
Stage II-IV
ns

图5

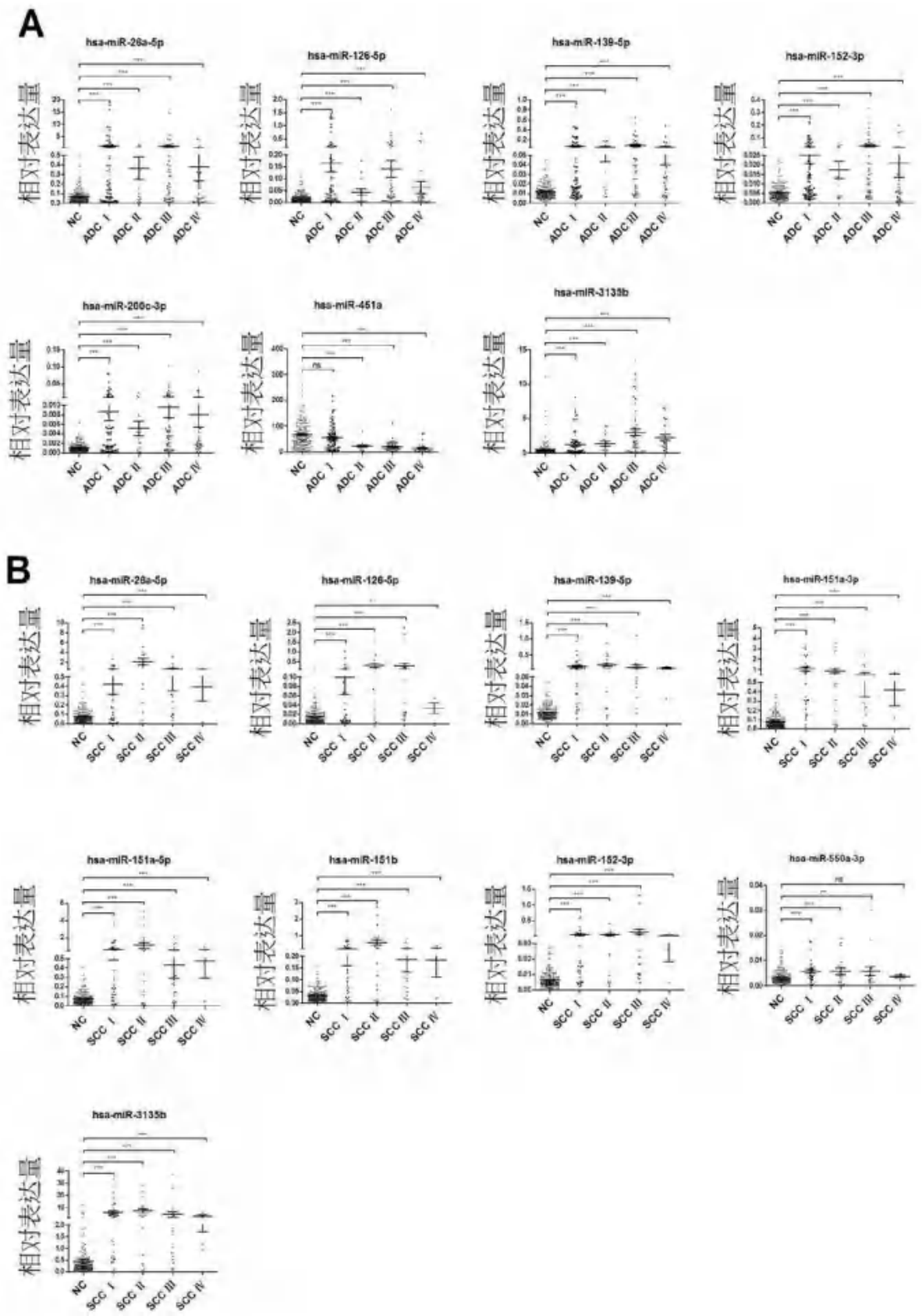

A
hsa-miR-26a-5p
hsa-miR-126-5p
hsa-miR-139-5p
hsa-miR-152-3p
hsa-miR-200c-3p
hsa-miR-451a
hsa-miR-3135b
B
hsa-miR-26a-5p
hsa-miR-126-5p
hsa-miR-139-5p
hsa-miR-151a-3p
hsa-miR-151a-5p
hsa-miR-151b
hsa-miR-152-3p
hsa-miR-550a-3p
hsa-miR-3135b
相对表达量
NC
ADC I
ADC II
ADC III
ADC IV
SCC I
SCC II
SCC III
SCC IV

图6

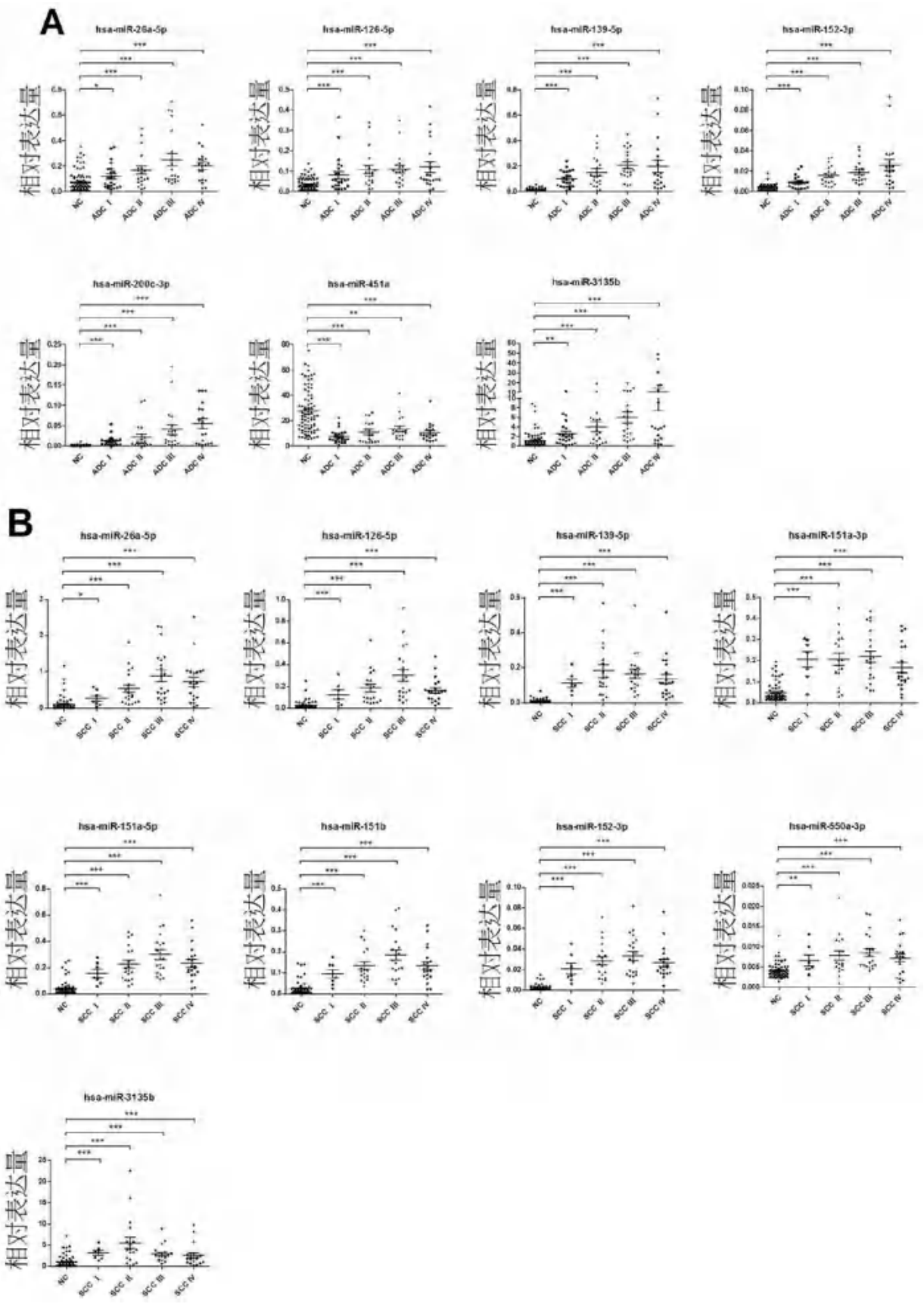
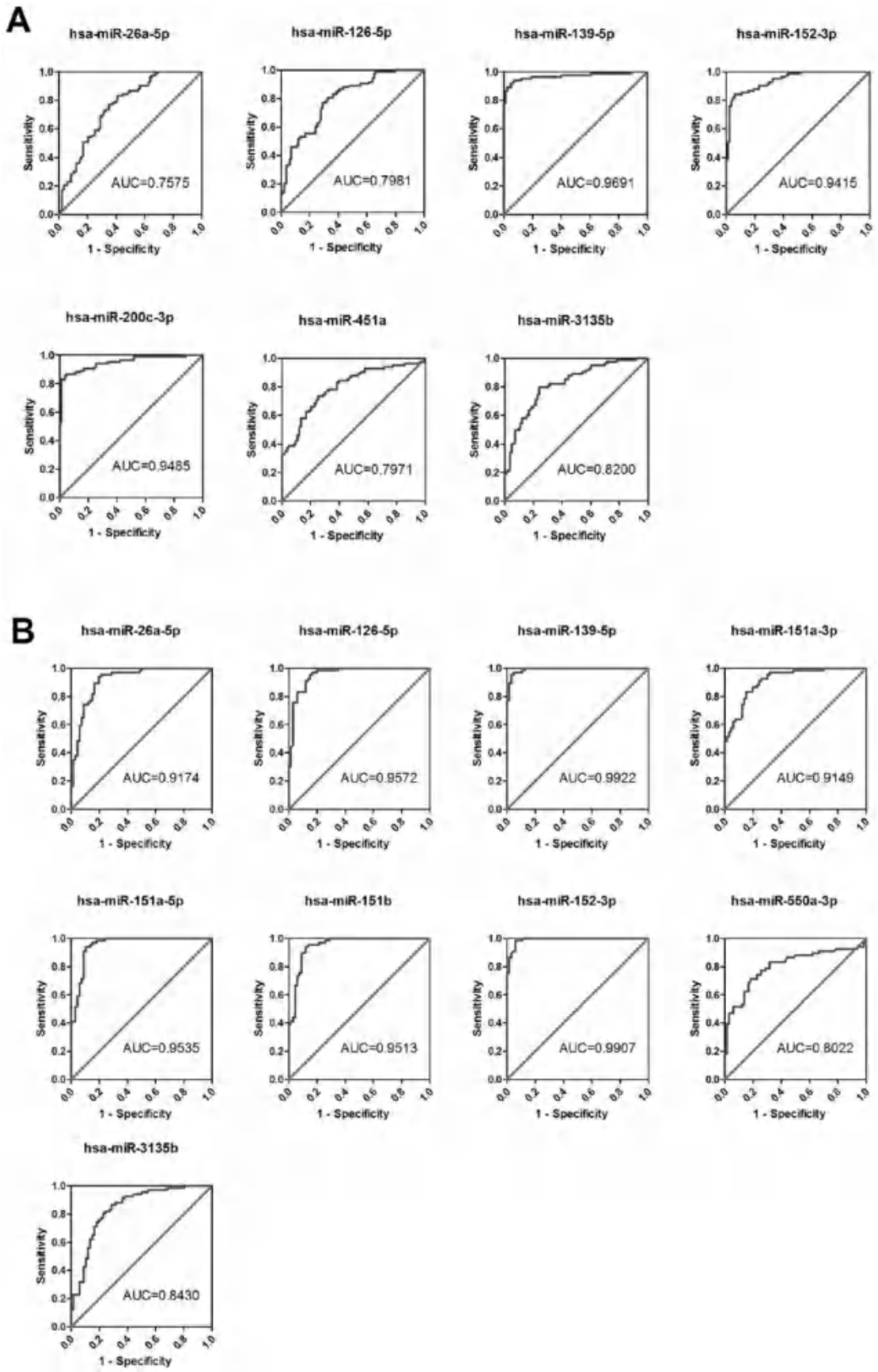

A
hsa-miR-26a-5p
hsa-miR-126-5p
hsa-miR-139-5p
hsa-miR-152-3p
hsa-miR-200c-3p
hsa-miR-451a
hsa-miR-3135b
相对表达量
NC
ADC I
ADC II
ADC III
ADC IV
B
hsa-miR-26a-5p
hsa-miR-126-5p
hsa-miR-139-5p
hsa-miR-151a-3p
hsa-miR-151a-5p
hsa-miR-151b
hsa-miR-152-3p
hsa-miR-550a-3p
hsa-miR-3135b
相对表达量
NC
SCC I
SCC II
SCC III
SCC IV

图7


A
hsa-miR-26a-5p
AUC=0.7575
hsa-miR-126-5p
AUC=0.7981
hsa-miR-139-5p
AUC=0.9691
hsa-miR-152-3p
AUC=0.9415
hsa-miR-200c-3p
AUC=0.9485
hsa-miR-451a
AUC=0.7971
hsa-miR-3135b
AUC=0.8200
B
hsa-miR-26a-5p
AUC=0.9174
hsa-miR-126-5p
AUC=0.9572
hsa-miR-139-5p
AUC=0.9922
hsa-miR-151a-3p
AUC=0.9149
hsa-miR-151a-5p
AUC=0.9535
hsa-miR-151b
AUC=0.9513
hsa-miR-152-3p
AUC=0.9907
hsa-miR-550a-3p
AUC=0.8022
hsa-miR-3135b
AUC=0.8430
Sensitivity
1 - Specificity

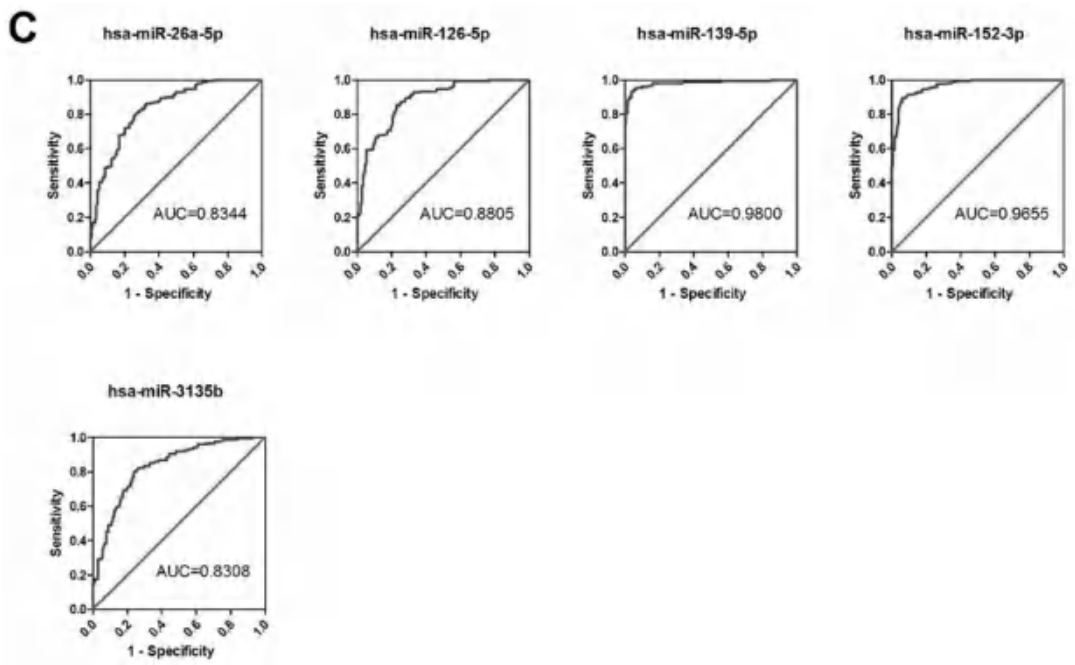

C
hsa-miR-26a-5p
AUC=0.8344
hsa-miR-126-5p
AUC=0.8805
hsa-miR-139-5p
AUC=0.9800
hsa-miR-152-3p
AUC=0.9655
hsa-miR-3135b
AUC=0.8308
Sensitivity
1 - Specificity

图8

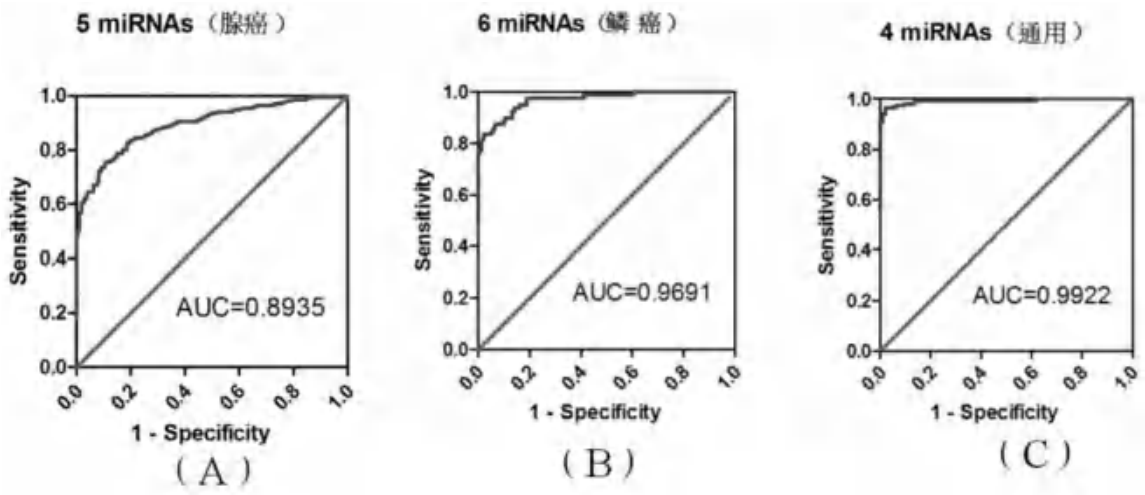

5 miRNAs（腺癌）
AUC=0.8935
(A)
6 miRNAs（鳞癌）
AUC=0.9691
(B)
4 miRNAs（通用）
AUC=0.9922
(C)
Sensitivity
1 - Specificity

图9