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(54) 발명의 명칭 **LRRK2 발현 감소용 화합물 및 방법**

(57) 요 약

세포 또는 동물에서 LRRK2 RNA의 양 또는 활성 감소용, 그리고 특정 사례에서 세포 또는 동물에서 LRRK2 단백질의 양 감소용 화합물, 방법, 및 약제학적 조성물이 제공된다. 상기 화합물, 방법, 및 약제학적 조성물은 신경퇴행성 질환의 적어도 5 하나의 징후 또는 특징을 개선하는데 유용하다. 그와 같은 징후 및 특징은 운동실조증, 신경병증, 및 응집체 형성을 포함한다. 그와 같은 신경퇴행성 질환은 파킨슨병을 포함한다.

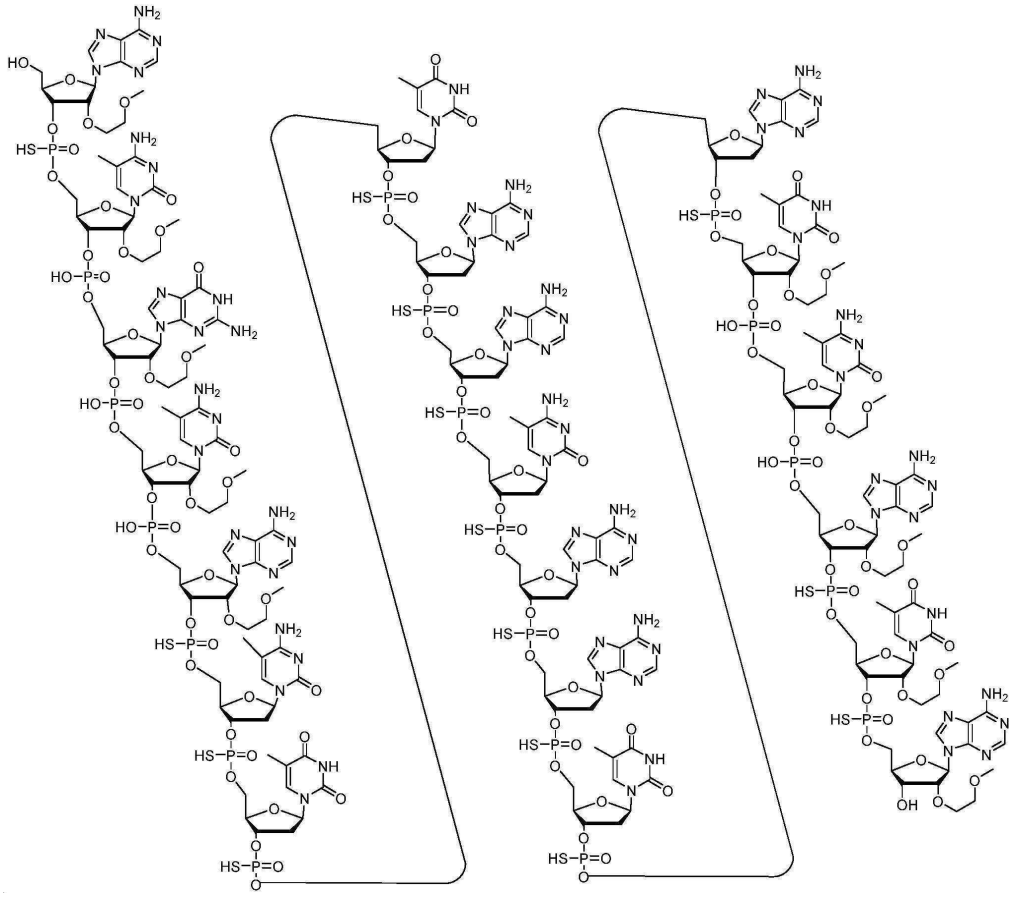
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명 세 서

청구범위

청구항 1

하기 화학 구조에 따른 변형된 올리고뉴클레오타이드:



(서열번호: 3590)

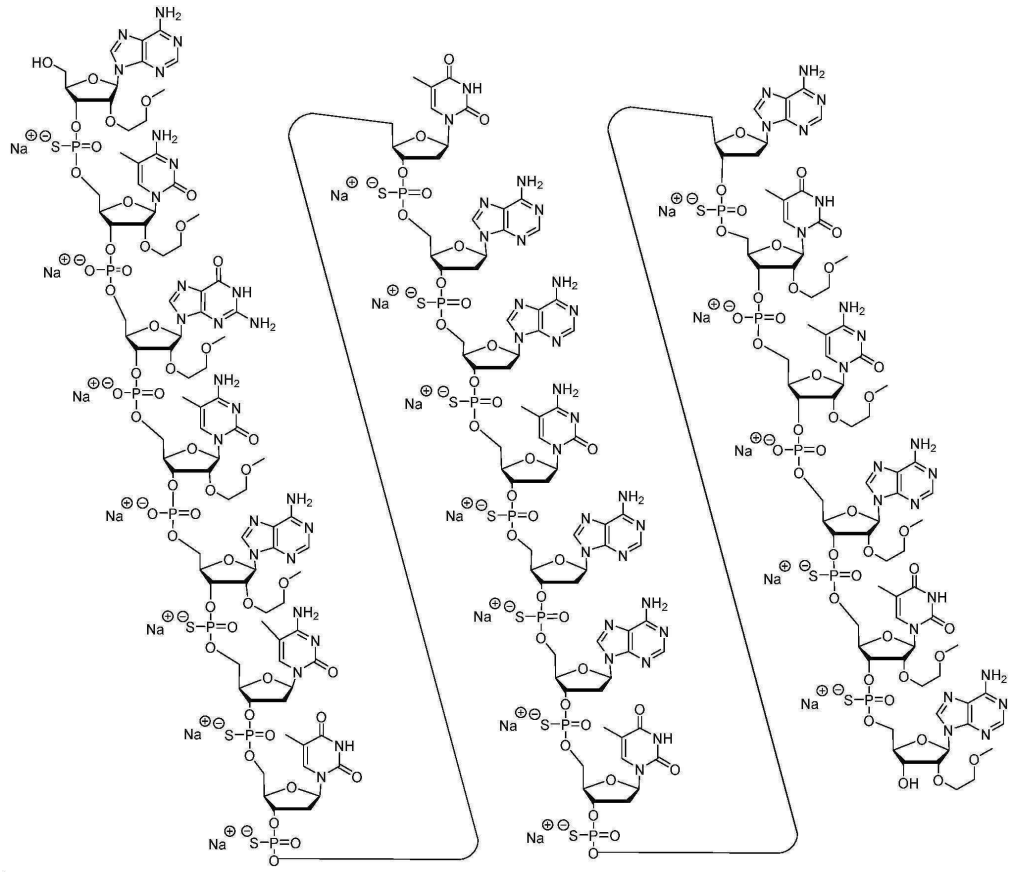
또는 이의 염.

청구항 2

제1항에 있어서, 나트륨 염 또는 칼륨 염인 변형된 올리고뉴클레오타이드.

청구항 3

하기 화학 구조에 따른 변형된 올리고뉴클레오타이드:



(서열번호: 3590).

청구항 4

하기 화학 표기법 (5'에서 3')에 따른 변형된 올리고뉴클레오타이드를 포함하는 올리고머 화합물:

Aes mCeo Geo mCeo Aes mCds Tds Tds Ads Ads mCds Ads Ads Tds Ads Teo mCeo Aes Tes Ae (서열번호: 3590);

여기서:

A = 아데닌 핵염기,

mC = 5-메틸 시토신 핵염기,

G = 구아닌 핵염기,

T = 티민 핵염기,

e = 2'-O$(CH_2)_2OCH_3$ 리보실 당 모이어티,

d = 2'-데옥시리보실 당 모이어티,

s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

o = 포스포디에스테르 인터뉴클레오사이드 연결기.

청구항 5

집단으로서, 제1항 내지 제3항 중 어느 한 항의 변형된 올리고뉴클레오타이드의 집단 또는 제4항의 올리고머 화합물의 집단이며, 여기서 변형된 올리고뉴클레오타이드의 포스포로티오에이트 인터뉴클레오사이드 연결기 모두가 스테레오랜덤인 집단.

청구항 6

제1항 내지 제3항 중 어느 한 항의 변형된 올리고뉴클레오타이드 또는 제4항의 올리고머 화합물 및 약제학적으로 허용가능한 희석제를 포함하는, 신경퇴행성 질환의 치료에 사용하기 위한 약제학적 조성물.

청구항 7

제6항에 있어서, 약제학적으로 허용가능한 희석제가 인공 뇌척수액 또는 포스페이트-완충 염수 (PBS)인 약제학적 조성물.

청구항 8

제7항에 있어서, 변형된 올리고뉴클레오타이드 또는 올리고머 화합물 및 인공 뇌척수액 또는 PBS로 본질적으로 이루어진 약제학적 조성물.

청구항 9

제5항의 집단 및 약제학적으로 허용가능한 희석제를 포함하는, 신경퇴행성 질환의 치료에 사용하기 위한 약제학적 조성물.

청구항 10

제9항에 있어서, 약제학적으로 허용가능한 희석제가 인공 뇌척수액 또는 포스페이트-완충 염수 (PBS)인 약제학적 조성물.

청구항 11

제10항에 있어서, 집단 및 인공 뇌척수액 또는 PBS로 본질적으로 이루어진 약제학적 조성물.

청구항 12

제1항 내지 제3항 중 어느 한 항의 변형된 올리고뉴클레오타이드 또는 제4항의 올리고머 화합물을 포함하는, 동물에서의 질환의 치료를 위한 약제학적 조성물이며, 여기서 질환이 신경퇴행성 질환인 약제학적 조성물.

청구항 13

제12항에 있어서, 치료가 세포에서 LRRK2의 발현을 감소시키는 것을 포함하는 것인 약제학적 조성물.

청구항 14

제13항에 있어서, 세포가 인간 세포인 약제학적 조성물.

청구항 15

제5항의 집단을 포함하는, 동물에서의 질환의 치료를 위한 약제학적 조성물이며, 여기서 질환이 신경퇴행성 질환인 약제학적 조성물.

청구항 16

제15항에 있어서, 치료가 세포에서 LRRK2의 발현을 감소시키는 것을 포함하는 것인 약제학적 조성물.

청구항 17

제16항에 있어서, 세포가 인간 세포인 약제학적 조성물.

청구항 18

제1항 내지 제3항 중 어느 한 항의 변형된 올리고뉴클레오타이드 또는 제4항의 올리고머 화합물을 포함하는, LRRK2와 연관된 질환의 치료를 위한 약제학적 조성물이며, 상기 치료는 LRRK2와 연관된 질환을 가지고 있거나 발병의 위험에 처한 개체에 치료 유효량의 변형된 올리고뉴클레오타이드 또는 올리고머 화합물을 투여하는 것을 포함하는 것인 약제학적 조성물이며, 여기서 LRRK2와 연관된 질환이 신경퇴행성 질환인 약제학적 조성물.

청구항 19

제18항에 있어서, 신경퇴행성 질환이 파킨슨병인 약제학적 조성물.

청구항 20

제18항에 있어서, 신경퇴행성 질환의 적어도 하나의 징후 또는 특징이 개선되는 것인 약제학적 조성물.

청구항 21

제19항에 있어서, 신경퇴행성 질환의 적어도 하나의 징후 또는 특징이 개선되는 것인 약제학적 조성물.

청구항 22

제20항에 있어서, 징후 또는 특징이 운동실조증, 신경병증, 및 응집체 형성 중 임의의 것인 약제학적 조성물.

청구항 23

제21항에 있어서, 징후 또는 특징이 운동실조증, 신경병증, 및 응집체 형성 중 임의의 것인 약제학적 조성물.

청구항 24

제5항의 집단을 포함하는, LRRK2와 연관된 질환의 치료를 위한 약제학적 조성물이며, 상기 치료는 LRRK2와 연관된 질환을 가지고 있거나 발병의 위험에 처한 개체에 치료 유효량의 집단을 투여하는 것을 포함하고, 여기서 LRRK2와 연관된 질환이 신경퇴행성 질환인 약제학적 조성물.

청구항 25

제24항에 있어서, 신경퇴행성 질환이 파킨슨병인 약제학적 조성물.

청구항 26

제24항에 있어서, 신경퇴행성 질환의 적어도 하나의 징후 또는 특징이 개선되는 것인 약제학적 조성물.

청구항 27

제25항에 있어서, 신경퇴행성 질환의 적어도 하나의 징후 또는 특징이 개선되는 것인 약제학적 조성물.

청구항 28

제26항에 있어서, 징후 또는 특징이 운동실조증, 신경병증, 및 응집체 형성 중 임의의 것인 약제학적 조성물.

청구항 29

제27항에 있어서, 징후 또는 특징이 운동실조증, 신경병증, 및 응집체 형성 중 임의의 것인 약제학적 조성물.

청구항 30

삭제

청구항 31

삭제

청구항 32

삭제

청구항 33

삭제

청구항 34

삭제

청구항 35

삭제

청구항 36

삭제

청구항 37

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청구항 38

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청구항 71

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청구항 72

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청구항 73

삭제

청구항 74

삭제

발명의 설명

기 술 분 야

[0001] **서열 목록**

[0002] 본원은 전자 형태의 서열 목록과 함께 출원 중이다. 서열 목록은, 크기가 1.12 MB인, 2019년 6월 14일 창작된, 파일명 BIOL0324WOSEQ_ST25.txt로서 제공된다. 서열 목록의 전자 형태의 정보는 본 명세서에 참고로 전체적으로 편입된다.

[0003] **분야**

[0004] 세포 또는 동물에서 류신-풍부 반복 키나제 2 (LRRK2) RNA의 양 또는 활성 감소용, 그리고 특정 사례에서 세포 또는 동물에서 LRRK2 단백질의 양 감소용 화합물, 방법, 및 약제학적 조성물이 제공된다. 상기 화합물, 방법, 및 약제학적 조성물은 신경퇴행성 질환의 적어도 하나의 징후 또는 특징을 개선하는데 유용하다. 그와 같은 징후 및 특징은 운동실조증, 신경병증, 및 응집체 형성을 포함한다. 그와 같은 신경퇴행성 질환은 파킨슨병을 포함한다.

배 경 기 술

[0005] LRRK2 유전자는 아르마딜로 반복 (ARM) 영역, 안키린 반복 (ANK) 영역, 류신-풍부 반복 (LRR) 도메인, 키나제 도메인, RAS 도메인, GTPase 도메인, 및 WD40 도메인을 가진 단백질을 인코딩한다. 단백질은 주로 세포질에서 존재하지만 또한 미토콘드리아 외막과 회합한다. LRRK2 단백질의 1개 단편은 류신이 풍부하고 신호 전달 및 세포골격 조립에서 관여될 수 있다. LRRK2 단백질의 다른 부분은 또한 단백질-단백질 상호작용에서 관여된다고 생각된다. 추가의 연구는 LRRK2 단백질이, 인산화 및 GTPase 활성을 포함하는, 키나제 활성으로서 공지된 효소 기능을 갖는다는 것을 명시한다. LRRK2는 바디 전반에 걸쳐 뇌 및 기타 조직에서 활성이다.

[0006] 전장 유전체 연관성 분석은 LRRK2와 파킨슨병 사이 연관을 발견하였다. 사실, LRRK2는 파킨슨병에 대한 최대 공

지된 유전 기여자이다. 그럼에도 불구하고, 파킨슨병은 유전병으로 간주되어 오지 않았다. 대부분의 파킨슨병은 특발성이다. 파킨슨병의 대략 10 퍼센트는 유전적 원인에 연결되어 왔다. LRRK2 유전자에서 돌연변이는, 총 파킨슨병 사례의 1 내지 2 퍼센트를 나타내는, 이러한 비교적 소그룹에서 파킨슨병의 가장 흔한 원인이다.

[0007] 현재 신경퇴행성 질환 예컨대, 비-LRRK2 매개된 파킨슨병을 포함하는, 파킨슨병 치료에 대하여 허용가능한 옵션은 부족하다. 그러므로 그러한 질환의 치료용 화합물, 방법, 및 약제학적 조성물을 제공하는 것이 본 명세서에서 목적이다.

발명의 내용

과제의 해결 수단

[0008] 세포 또는 동물에서 LRRK2 RNA의 양 또는 활성 감소용, 그리고 특정 구현예에서 LRRK2 단백질의 양 감소용 화합물, 방법, 및 약제학적 조성물은 본 명세서에 제공된다. 특정 구현예에서, 동물은 신경퇴행성 질환을 가지고 있다. 특정 구현예에서, 동물은 파킨슨병을 가지고 있다. 특정 구현예에서, LRRK2 RNA의 발현 감소에 유용한 화합물은 올리고머성 화합물이다. 특정 구현예에서, LRRK2 RNA의 발현 감소에 유용한 화합물은 변형된 올리고뉴클레오타이드이다.

[0009] 신경퇴행성 질환의 적어도 하나의 징후 또는 특징의 개선에 유용한 방법은 또한 제공된다. 특정 구현예에서, 신경퇴행성 질환은 파킨슨병이다. 특정 구현예에서 파킨슨병은 어느 한쪽 LRRK2 매개된 파킨슨병 또는 비-LRRK2 매개된 파킨슨병이다. 특정 구현예에서, 징후 또는 특징은 운동실조증, 신경병증, 및 응집체 형성을 포함한다. 특정 구현예에서, 이들 징후의 개선은 개선된 운동 기능, 감소된 신경병증, 및 응집체의 수에서 감소를 초래한다.

발명을 실시하기 위한 구체적인 내용

[0010] 상술한 일반적인 설명 및 하기 상세한 설명 둘 모두가 단지 예시적이고 설명적이며 제한적이지 않는다는 것을 이해해야 한다. 본 명세서에서, 단수의 사용은 달리 구체적으로 언급되지 않는 한 복수를 포함한다. 본 명세서에 사용된 바와 같이, "또는"의 사용은 달리 언급되지 않는 한 "및/또는"을 의미한다. 게다가, 용어 "포함하는" 뿐만 아니라 다른 형태, 예컨대 "포함한다" 및 "포함된"의 사용은 비제한적이다. 또한, 용어 예컨대 "요소" 또는 "성분"은, 달리 구체적으로 언급되지 않는 한, 1개의 유닛을 포함하는 요소 및 성분 그리고 1개 초과의 서브유닛을 포함하는 요소 및 성분 둘 모두를 포괄한다.

[0011] 본 명세서에 사용된 섹션 제목은 단지 조직상의 목적이고 기재된 요지 제한으로서 해석되지 않아야 한다. 비제한적으로, 특허, 특허 출원, 기사, 서적, 및 논문을 포함하는, 본원에서 인용된, 모든 문서, 또는 문서의 부분들은 본 명세서에 논의된 문서의 부분으로, 뿐만 아니라 전체적으로 참고로 이로써 명시적으로 편입된다.

[0012] *정의*

[0013] 구체적 정의가 제공되지 않는 한, 본 명세서에 기재된 분석 화학, 유기 합성 화학, 그리고 의료 화학 및 약화학의 절차 및 기술, 그리고 상기와 관련하여 사용된 명명법은 당해 기술에서 흔하게 사용되고 널리 공지된 것들이다. 허용되는 경우, 본 개시내용에서 전반에 걸쳐 지칭된 모든 특허, 출원, 공개 출원 및 기타 공보 그리고 기타 데이터는 본 명세서에 참고로 전체적으로 편입된다.

[0014] 달리 나타내지 않는 한, 하기 용어는 하기 의미를 갖는다:

[0015] **정의**

[0016] 본 명세서에 사용된 바와 같이, "2'-데옥시뉴클레오사이드"는, 자연 발생 데옥시리보핵산 (DNA)에서 발견된 대로, 2'-H(H) 데옥시리보실 당 모이어티를 포함하는 뉴클레오사이드를 의미한다. 특정 구현예에서, 2'-데옥시뉴클레오사이드는 변형된 핵염기를 포함할 수 있거나 RNA 핵염기 (우라실)을 포함할 수 있다.

[0017] 본 명세서에 사용된 바와 같이, "2'-치환된 뉴클레오사이드"는 2'-치환된 당 모이어티를 포함하는 뉴클레오사이드를 의미한다. 본 명세서에 사용된 바와 같이, 당 모이어티와 관련하여 "2'-치환된"은 H 또는 OH 이외 적어도 하나의 2'-치환기를 포함하는 당 모이어티를 의미한다.

[0018] 본 명세서에 사용된 바와 같이, "5-메틸 시토신"은 5번 위치에 부착된 메틸기로 변형된 시토신을 의미한다. 5-메틸 시토신은 변형된 핵염기이다.

[0019] 본 명세서에 사용된 바와 같이, "투여하는"은 약제학적 제제를 동물에 제공하는 것을 의미한다.

[0020] 본 명세서에 사용된 바와 같이, "동물"은 인간 또는 비-인간 동물을 의미한다.

[0021] 본 명세서에 사용된 바와 같이, "안티센스 활성"은 그것의 표적 핵산에 대한 안티센스 화합물의 하이브리드화에 기인하는 임의의 검출가능한 및/또는 측정가능한 변화를 의미한다. 특정 구현예에서, 안티센스 활성은 안티센스 화합물의 부재 하에서 표적 핵산 수준 또는 표적 단백질 수준에 비교된 그와 같은 표적 핵산에 의해 인코딩된 표적 핵산 또는 단백질의 양 또는 발현에서 감소이다.

[0022] 본 명세서에 사용된 바와 같이, "안티센스 화합물"은 하나 이상의 안티센스 활성을 달성할 수 있는 올리고머성 화합물을 의미한다.

[0023] 본 명세서에 사용된 바와 같이, 치료와 관련하여 "개선한다"는 치료의 부재 하에서 동일한 증상에 비하여 적어도 하나의 증상에서 개선을 의미한다. 특정 구현예에서, 개선은 증상의 중증도 또는 빈도에서 감소 또는 증상의 중증도 또는 빈도에서 지연된 개시 또는 진행의 저속화이다. 특정 구현예에서, 징후 또는 특징은 운동실조증, 신경병증, 및 응집체 형성이다. 특정 구현예에서, 이들 증상의 개선은 개선된 운동 기능, 감소된 신경병증, 및 응집체의 수에서 감소를 초래한다.

[0024] 본 명세서에 사용된 바와 같이, "이환형 뉴클레오사이드" 또는 "BNA"는 이환형 당 모이어티를 포함하는 뉴클레오사이드를 의미한다.

[0025] 본 명세서에 사용된 바와 같이, "이환형 당" 또는 "이환형 당 모이어티"는 2개의 고리를 포함하는 변형된 당 모이어티를 의미하고, 여기서 제2 고리는 제1 고리에서 원자들 중 2개를 연결하는 브릿지를 통해 형성되어 그것에 의해 이환형 구조를 형성한다. 특정 구현예에서, 이환형 당 모이어티의 제1 고리는 푸라노실 모이어티이다. 특정 구현예에서, 이환형 당 모이어티는 푸라노실 모이어티를 포함하지 않는다.

[0026] 본 명세서에 사용된 바와 같이, "절단가능한 모이어티"는, 예를 들어, 세포, 동물, 또는 인간 내부에서, 생리적 조건 하에서 절단되는 원자의 그룹 또는 결합을 의미한다.

[0027] 본 명세서에 사용된 바와 같이, 올리고뉴클레오타이드와 관련하여 "상보성"은 올리고뉴클레오타이드 또는 이의 하나 이상의 영역의 핵염기 및 또 다른 핵산 또는 이의 하나 이상의 영역의 핵염기의 적어도 70%가 올리고뉴클레오타이드 및 다른 핵산의 핵염기 서열이 대향하는 방향으로 정렬되는 경우 서로와 수소 결합할 수 있다는 것을 의미한다. 상보성 핵염기는 서로와 수소 결합을 형성할 수 있는 핵염기를 의미한다. 상보성 핵염기 쌍은 아데닌 (A) 및 티민 (T), 아데닌 (A) 및 우라실 (U), 시토신 (C) 및 구아닌 (G), 5-메틸 시토신 (mC) 및 구아닌 (G)를 포함한다. 상보성 올리고뉴클레오타이드 및/또는 핵산은 각 뉴클레오사이드에 핵염기 상보성을 가질 필요가 없다. 오히려, 일부 미스매치는 용인된다. 본 명세서에 사용된 바와 같이, 올리고뉴클레오타이드와 관련하여 "완전하게 상보성" 또는 "100% 상보성"은 올리고뉴클레오타이드가 또 다른 올리고뉴클레오타이드 또는 올리고뉴클레오타이드의 각 뉴클레오사이드의 핵산에 상보성이라는 것을 의미한다.

[0028] 본 명세서에 사용된 바와 같이, "컨쥬게이트 그룹"은 올리고뉴클레오타이드에 직접적으로 부착되는 원자의 그룹을 의미한다. 컨쥬게이트 그룹은 컨쥬게이트 모이어티를 올리고뉴클레오타이드에 부착시키는 컨쥬게이트 링커 및 컨쥬게이트 모이어티를 포함한다.

[0029] 본 명세서에 사용된 바와 같이, "컨쥬게이트 링커"는 컨쥬게이트 모이어티를 올리고뉴클레오타이드에 연결시키는 적어도 하나의 결합을 포함하는 원자의 그룹 또는 단일 결합을 의미한다.

[0030] 본 명세서에 사용된 바와 같이, "컨쥬게이트 모이어티"는 컨쥬게이트 링커를 통해 올리고뉴클레오타이드에 부착되는 원자의 그룹을 의미한다.

[0031] 본 명세서에 사용된 바와 같이, 올리고뉴클레오타이드의 맥락에서 "연속적"은 서로에 바로 인접한 뉴클레오사이드, 핵염기, 당 모이어티, 또는 인터뉴클레오사이드 연결기를 지칭한다. 예를 들어, "연속적 핵염기"는 서열에서 서로에 바로 인접한 핵염기를 의미한다.

[0032] 본 명세서에 사용된 바와 같이, "구속된 에틸" 또는 "cEt" 또는 "cEt 변형된당"은 이환형 당의 제2 고리가 β-D 리보실 당 모이어티의 4'-탄소 및 2'-탄소를 연결하는 브릿지를 통해 형성되는 β-D 리보실 이환형 당 모이어티를 의미하고, 여기서 상기 브릿지는 식 4'-$CH(CH_3)$-O-2'를 갖고, 상기 브릿지의 메틸기는 S 배치형태이다.

[0033] 본 명세서에 사용된 바와 같이, "cEt 뉴클레오사이드"는 cEt 변형된 당을 포함하는 뉴클레오사이드를 의미한다.

[0034] 본 명세서에 사용된 바와 같이, "키랄 풍부 집단"은 동일한 분자식의 복수의 분자를 의미하고, 여기서 특정 키랄 중심에 특정 입체화학적 배치형태를 함유하는 집단 내에서 분자의 수 또는 백분율은 특정 키랄 중심이 스테레오랜덤이면 집단 내에서 동일한 특정 키랄 중심에 동일한 특정 입체화학적 배치형태를 함유할 것으로 기대된 분자의 수 또는 백분율 초과이다. 각 분자 내에서 다중 키랄 중심을 가지고 있는 분자의 키랄 풍부 집단은 하나 이상의 스테레오랜덤 키랄 중심을 함유할 수 있다. 특정 구현예에서, 분자는 변형된 올리고뉴클레오타이드이다. 특정 구현예에서, 분자는 변형된 올리고뉴클레오타이드를 포함하는 화합물이다.

[0035] 본 명세서에 사용된 바와 같이, "갭머"는 하나 이상의 뉴클레오사이드를 가지고 있는 외부 영역 사이 위치한 RNase H 절단을 지원하는 복수의 뉴클레오사이드를 가지고 있는 내부 영역을 포함하는 변형된 올리고뉴클레오타이드를 의미하고, 여기서 내부 영역을 포함하는 뉴클레오사이드는 외부 영역을 포함하는 뉴클레오사이드 또는 뉴클레오사이드들과 화학적으로 구별된다. 내부 영역은 "갭"으로서 지칭될 수 있고 외부 영역은 "윙"으로서 지칭될 수 있다. 달리 나타내지 않는 한, "갭머"는 당 모티프를 지칭한다. 달리 나타내지 않는 한, 갭머의 갭의 뉴클레오사이드의 당 모이어티는 미변형된 2'-데옥시리보실이다. 따라서, 용어 "MOE 갭머"는 2'-데옥시뉴클레오사이드의 양쪽 윙 및 갭에서 2'-MOE 뉴클레오사이드의 당 모티프를 가지고 있는 갭머를 나타낸다. 달리 나타내지 않는 한, MOE 갭머는 하나 이상의 변형된 인터뉴클레오사이드 연결기 및/또는 변형된 핵염기를 포함할 수 있고 그와 같은 변형은 당 변형의 갭머 패턴을 반드시 따르지 않는다.

[0036] 본 명세서에 사용된 바와 같이, "핫스팟 영역"은 표적 핵산의 양 또는 활성의 올리고머성 화합물-매개된 감소를 할 수 있는 표적 핵산 상에서 핵염기의 범위이다.

[0037] 본 명세서에 사용된 바와 같이, "하이브리드화"는 상보성 올리고뉴클레오타이드 및/또는 핵산의 짝짓기 또는 어닐링을 의미한다. 특정 기전에 제한되지 않으면서, 하이브리드화의 가장 흔한 기전은, 상보성 핵염기 사이, 왓슨-크릭, 휴그스틴 또는 역전된 휴그스틴 수소 결합일 수 있는, 수소 결합을 포함한다.

[0038] 본 명세서에 사용된 바와 같이, 용어 "인터뉴클레오사이드 연결기"는 올리고뉴클레오타이드에서 인접한 뉴클레오사이드 사이 공유 연결기이다. 본 명세서에 사용된 바와 같이 "변형된 인터뉴클레오사이드 연결기"는 포스포디에스테르 인터뉴클레오사이드 연결기 이외 임의의 인터뉴클레오사이드 연결기를 의미한다. "포스포로티오에이트 인터뉴클레오사이드 연결기"는 포스포디에스테르 인터뉴클레오사이드 연결기의 비-브릿징 산소 원자들 중 1개가 황 원자로 대체되는 변형된 인터뉴클레오사이드 연결기이다.

[0039] 본 명세서에 사용된 바와 같이, "링커-뉴클레오사이드"는, 어느 한쪽 직접적으로 또는 간접적으로, 올리고뉴클레오타이드를 컨쥬게이트 모이어티에 연결시키는 뉴클레오사이드를 의미한다. 링커-뉴클레오사이드는 올리고머성 화합물의 컨쥬게이트 링커 내에서 위치한다. 링커-뉴클레오사이드는 이들이 올리고뉴클레오타이드로 연속적일지라도 올리고머성 화합물의 올리고뉴클레오타이드 부분의 일부로 간주되지 않는다.

[0040] 본 명세서에 사용된 바와 같이, "비-이환형 변형된 당 모이어티"는, 제2 고리를 형성하기 위해 당의 2개 원자 사이 브릿지를 형성하지 않는, 변형, 예컨대 치환체를 포함하는 변형된 당 모이어티를 의미한다.

[0041] 본 명세서에 사용된 바와 같이, "미스매치" 또는 "비-상보성"은 제1 및 제2 올리고뉴클레오타이드가 정렬되는 경우 제2 올리고뉴클레오타이드 또는 표적 핵산의 상응하는 핵염기와 상보성이지 않은 제1 올리고뉴클레오타이드의 핵염기를 의미한다.

[0042] 본 명세서에 사용된 바와 같이, "MOE"는 메톡시에틸을 의미한다. "2'-MOE" 또는 "2'-MOE 변형된 당"은 리보실 당 모이어티의 2'-OH 기 대신에 2'-$OCH_2CH_2OCH_3$ 기를 의미한다. 본 명세서에 사용된 바와 같이, "2'-MOE 뉴클레오사이드"는 2'-MOE 변형된 당을 포함하는 뉴클레오사이드를 의미한다.

[0043] 본 명세서에 사용된 바와 같이, "모티프"는 올리고뉴클레오타이드에서 미변형된 및/또는 변형된 당 모이어티, 핵염기, 및/또는 인터뉴클레오사이드 연결기의 패턴을 의미한다.

[0044] 본 명세서에 사용된 바와 같이, "RNA"는 달리 특정되지 않는 한 pre-mRNA 및 성숙 mRNA를 포함하는 그리고 단백질을 인코딩하는 RNA 전사체를 의미한다.

[0045] 본 명세서에 사용된 바와 같이, "신경퇴행성 질환"은, 운동 기능의 소실 및 뉴런의 사망을 포함하는, 기능 또는 구조의 진행형 소실에 의해 표시된 병태를 의미한다. 특정 구현예에서, 신경퇴행성 질환은 파킨슨병이다. 특정 구현예에서, 파킨슨병은 LRRK2 매개된 파킨슨병 또는 비-LRRK2 매개된 파킨슨병일 수 있다.

[0046] "비-LRRK2 매개된 파킨슨병"은 원인성 LRRK2 유전적 돌연변이와 연관되지 않은 파킨슨병의 진단이다. 원인성

LRRK2 유전적 돌연변이는 G2019S, R1441C, R1441G, I2020T, 및 Y1699C를 포함한다. 파킨슨병의 진단은 개체의 의료 이력 평가, 징후 및 증상의 관찰, 및 표준 임상 시험 또는 평가를 포함하는 임의의 방법에 의해 달성될 수 있다. LRRK2와 연관된 돌연변이, 예컨대 G2019S, R1441C, R1441G, I2020T, 및 Y1699C에 대한 유전 시험은 개체가 비-LRRK2 매개된 파킨슨병을 가지고 있는지 여부를 밝혀낼 수 있다. 파킨슨병의 진단을 가지고 있는, 그러나 원인성 LRRK2 돌연변이가 없는 개체는 비-LRRK2 매개된 파킨슨병을 가지고 있다. "비-LRRK2 매개된 파킨슨병을 가지고 있는 동물의 확인"은 파킨슨병으로 진단된 또는 원인성 LRRK2 돌연변이 없이 파킨슨병을 발병할 것으로 예고된 동물을 확인하는 것을 의미한다.

[0047] 본 명세서에 사용된 바와 같이, "핵염기"는 미변형된 핵염기 또는 변형된 핵염기를 의미한다. 본 명세서에 사용된 바와 같이 "미변형된 핵염기"는 아데닌 (A), 티민 (T), 시토신 (C), 우라실 (U), 또는 구아닌 (G)이다. 본 명세서에 사용된 바와 같이, "변형된 핵염기"는 적어도 하나의 미변형된 핵염기와 짝짓기할 수 있는 미변형된 A, T, C, U, 또는 G 이외 원자의 그룹이다. "5-메틸 시토신"은 변형된 핵염기이다. 보편적인 염기는 5개의 미변형된 핵염기들 중 어느 하나와 짝짓기할 수 있는 변형된 핵염기이다. 본 명세서에 사용된 바와 같이, "핵염기 서열"은 임의의 당 또는 인터뉴클레오사이드 연결기 변형과 독립적인 핵산 또는 올리고뉴클레오타이드에서 연속적 핵염기의 순서를 의미한다.

[0048] 본 명세서에 사용된 바와 같이, "뉴클레오사이드"는 핵염기 및 당 모이어티를 포함하는 화합물을 의미한다. 핵염기 및 당 모이어티 각각은, 독립적으로, 미변형되거나 변형된다. 본 명세서에 사용된 바와 같이, "변형된 뉴클레오사이드"는 변형된 핵염기 및/또는 변형된 당 모이어티를 포함하는 뉴클레오사이드를 의미한다. 변형된 뉴클레오사이드는, 핵염기가 부족한, 무염기성 뉴클레오사이드를 포함한다. "연결된 뉴클레오사이드"는 연속적 서열에서 연결되는 뉴클레오사이드이다 (즉 추가의 뉴클레오사이드는 연결되는 것들 사이에서 존재하지 않는다).

[0049] 본 명세서에 사용된 바와 같이, "올리고머성 화합물"은 올리고뉴클레오타이드 및 선택적으로 하나 이상의 추가의 특징, 예컨대 컨쥬게이트 그룹 또는 말단기를 의미한다. 올리고머성 화합물은 제1 올리고머성 화합물에 상보성인 제2 올리고머성 화합물과 짝짓기될 수 있거나 짝짓기되지 않을 수 있다. "단일가닥 올리고머성 화합물"은 짝짓기되지 않은 올리고머성 화합물이다. 용어 "올리고머성 듀플렉스"는 상보성 핵염기 서열을 가지고 있는 2개의 올리고머성 화합물에 의해 형성된 듀플렉스를 의미한다. 올리고머성 듀플렉스의 각 올리고머성 화합물은 "듀플렉스된 올리고머성 화합물"로서 지칭될 수 있다.

[0050] 본 명세서에 사용된 바와 같이, "올리고뉴클레오타이드"는 인터뉴클레오사이드 연결기를 통해 연결된 결합 뉴클레오사이드의 가닥을 의미하고, 상기 각 뉴클레오사이드 및 인터뉴클레오사이드 연결기는 변형될 수 있거나 미변형될 수 있다. 달리 나타내지 않는 한, 올리고뉴클레오타이드는 8-50개의 연결된 뉴클레오사이드로 이루어진다. 본 명세서에 사용된 바와 같이, "변형된 올리고뉴클레오타이드"는 올리고뉴클레오타이드를 의미하고, 상기 적어도 하나의 뉴클레오사이드 또는 인터뉴클레오사이드 연결기는 변형된다. 본 명세서에 사용된 바와 같이, "미변형된 올리고뉴클레오타이드"는 임의의 뉴클레오사이드 변형 또는 인터뉴클레오사이드 변형을 포함하지 않는 올리고뉴클레오타이드를 의미한다.

[0051] 본 명세서에 사용된 바와 같이, "약제학적으로 허용가능한 담체 또는 희석제"는 동물에 투여하기에 있어서 사용에 적당한 임의의 서브스턴스를 의미한다. 특정 상기 담체는 약제학적 조성물이, 예를 들어, 대상체에 의한 경구 섭취를 위하여 정제, 알약, 당의정, 캡슐, 액체, 겔, 시럽, 슬러리, 현탁액 및 로젠지로서 제형화되게 할 수 있다. 특정 구현예에서, 약제학적으로 허용가능한 담체 또는 희석제는 멸균수, 멸균 염수, 멸균 완충 용액 또는 멸균 인공 뇌척수액이다.

[0052] 본 명세서에 사용된 바와 같이 "약제학적으로 허용가능한 염"은 화합물의 생리적으로 및 약제학적으로 허용가능한 염을 의미한다. 약제학적으로 허용가능한 염은 모 화합물의 원하는 생물학적 활성을 보유하고 거기에 원하지 않는 독물학적 효과를 부여하지 않는다.

[0053] 본 명세서에 사용된 바와 같이 "약제학적 조성물"은 대상체에게 투여하기에 적당한 서브스턴스의 혼합물을 의미한다. 예를 들어, 약제학적 조성물은 올리고머성 화합물 및 멸균 수용액을 포함할 수 있다. 특정 구현예에서, 약제학적 조성물은 특정 세포주내 자유 흡수 검정에서 활성을 보여준다.

[0054] 본 명세서에 사용된 바와 같이 "전구약물"은 동물 또는 이의 세포 내에서 상이한 형태로 전환되는 바디 외부에서 형태로의 치료적 제제를 의미한다. 전형적으로 동물 내에서 전구약물의 전환은 세포 또는 조직에서 존재하는 효소 (예를 들면, 내인성 또는 바이러스 효소) 또는 화학물질의 작용에 의해 및/또는 생리적 조건에 의해 촉진된다.

[0055] 본 명세서에 사용된 바와 같이, "양 또는 활성 감소 또는 억제"는 미처리된 또는 대조군 샘플내 전사적 발현 또는 활성에 비하여 전사적 발현 또는 활성의 감소 또는 봉쇄를 지칭하고 전사적 발현 또는 활성의 총 제거를 반드시 나타내지 않는다.

[0056] 본 명세서에 사용된 바와 같이, "RNAi 화합물"은, 적어도 부분적으로, RISC 또는 Ago2를 통해 작용하여 표적 핵산 및/또는 표적 핵산에 의해 인코딩된 단백질을 조절하는 안티센스 화합물을 의미한다. RNAi 화합물은, 비제한적으로 이중가닥 siRNA, 단일가닥 RNA (ssRNA), 및 마이크로RNA 모방체를 포함하는, 마이크로RNA를 포함한다. 특정 구현예에서, RNAi 화합물은 표적 핵산의 양, 활성, 및/또는 스플라이싱을 조절한다. 용어 RNAi 화합물은 RNase H를 통해 작용하는 안티센스 화합물을 배제한다.

[0057] 본 명세서에 사용된 바와 같이, 올리고뉴클레오타이드와 관련하여 "자기-상보성"은 자체에 적어도 부분적으로 하이브리드화하는 올리고뉴클레오타이드를 의미한다.

[0058] 본 명세서에 사용된 바와 같이, "siRNA"는 2개의 역-평행 및 실질적으로 상보성 핵산 가닥을 포함하는 듀플렉스 구조를 가지고 있는 리보핵산 분자를 지칭한다. 듀플렉스 구조를 형성하는 2개의 가닥은 1개의 대형 RNA 분자의 상이한 부분일 수 있거나, 이들은 별도 RNA 분자일 수 있다. 2개의 가닥이 1개의 대형 분자의 일부이고, 그러므로 듀플렉스 구조를 형성하는 1개 가닥의 3'-말단과 각각의 다른 가닥의 5' 말단 사이 연속적 핵염기에 의해 연결되는 경우, 연결하는 RNA 사슬은 "헤어핀 루프"로서 지칭된다. RNA 가닥은 뉴클레오타이드의 동일한 또는 상이한 수를 가질 수 있다.

[0059] 본 명세서에 사용된 바와 같이, "표준 세포 검정"은 실시예 4에서 기재된 검정 및 이의 합리적인 변동을 의미한다.

[0060] 본 명세서에 사용된 바와 같이, "표준 생체내 검정"은 실시예 14에서 기재된 실험, 및 이의 합리적인 변동을 의미한다.

[0061] 본 명세서에 사용된 바와 같이, 동일한 분자식의 분자의 집단의 맥락에서 "스테레오랜덤 키랄 중심"은 랜덤 입체화학적 배치형태를 가지고 있는 키랄 중심을 의미한다. 예를 들어, 스테레오랜덤 키랄 중심을 포함하는 분자의 집단에서, 스테레오랜덤 키랄 중심의 (S) 배치형태를 가지고 있는 분자의 수는 스테레오랜덤 키랄 중심의 (R) 배치형태를 가지고 있는 분자의 수일 수 있지만 반드시 동일하지 않다. 키랄 중심의 입체화학적 배치형태는 입체화학적 배치형태를 제어하기 위해 설계되지 않은 합성 방법의 결과인 경우 랜덤으로 간주된다. 특정 구현예에서, 스테레오랜덤 키랄 중심은 스테레오랜덤 포스포로티오에이트 인터뉴클레오사이드 연결기이다.

[0062] 본 명세서에 사용된 바와 같이, "당 모이어티"는 미변형된 당 모이어티 또는 변형된 당 모이어티를 의미한다. 본 명세서에 사용된 바와 같이, "미변형된 당 모이어티"는, RNA에서 발견된 대로 2'-OH(H) 리보실 모이어티 ("미변형된 RNA 당 모이어티"), 또는 DNA에서 발견된 대로, 2'-H(H) 데옥시리보실 모이어티 ("미변형된 DNA 당 모이어티")를 의미한다. 미변형된 당 모이어티는 1', 3', 및 4' 위치의 각각에 1개의 수소, 3' 위치에 산소, 및 5' 위치에 2개의 수소를 갖는다. 본 명세서에 사용된 바와 같이, "변형된 당 모이어티" 또는 "변형된 당"은 변형된 푸라노실 당 모이어티 또는 당 대리물을 의미한다.

[0063] 본 명세서에 사용된 바와 같이, "당 대리물"은 올리고뉴클레오타이드에서 핵염기를 또 다른 그룹, 예컨대 인터뉴클레오사이드 연결기, 컨쥬게이트 그룹, 또는 말단기에 결합시킬 수 있는 푸라노실 모이어티 이외를 가지고 있는 변형된 당 모이어티를 의미한다. 당 대리물을 포함하는 변형된 뉴클레오사이드는 올리고뉴클레오타이드 내에서 하나 이상의 위치 속에 편입될 수 있고 그와 같은 올리고뉴클레오타이드는 상보성 올리고머성 화합물 또는 표적 핵산에 하이브리드화할 수 있다.

[0064] 본 명세서에 사용된 바와 같이, "표적 핵산" 및 "표적 RNA"는 안티센스 화합물이 작용하도록 설계되는 핵산을 의미한다.

[0065] 본 명세서에 사용된 바와 같이, "표적 영역"은 올리고머성 화합물이 하이브리드화하도록 설계되는 표적 핵산의 일 부분을 의미한다.

[0066] 본 명세서에 사용된 바와 같이, "말단기"는 올리고뉴클레오타이드의 말단에 공유적으로 연결되는 원자의 그룹 또는 화학기를 의미한다.

[0067] 본 명세서에 사용된 바와 같이, "치료적 유효량"은 동물에게 치료적 이점을 제공하는 약제학적 제제의 양을 의미한다. 예를 들어, 치료적 유효량은 질환의 증상을 개선한다.

[0068] **특정 구현예**

[0069] 본 개시내용은 하기 비제한 번호로 매겨진 구현예를 제공한다:

[0070] 구현예 1. 12 내지 50개의 연결된 뉴클레오사이드로 이루어지는 변형된 올리고뉴클레오타이드를 포함하는 올리고머성 화합물이며, 상기 변형된 올리고뉴클레오타이드의 핵염기 서열이 LRRK2 핵산의 동일 길이 부분에 적어도 90% 상보성이고, 상기 변형된 올리고뉴클레오타이드가 변형된 당, 당 대리물, 및 변형된 인터뉴클레오사이드 연결기로부터 선택된 적어도 하나의 변형을 포함하는, 올리고머성 화합물.

[0071] 구현예 2: 12 내지 50개의 연결된 뉴클레오사이드로 이루어지고 서열번호: 30-3847의 핵염기 서열 중 임의의 것의 적어도 12, 적어도 13, 적어도 14, 적어도 15, 적어도 16, 적어도 17, 적어도 18, 적어도 19, 또는 적어도 20개의 연속적 핵염기를 포함하는 핵염기 서열을 가지고 있는 변형된 올리고뉴클레오타이드를 포함하는 올리고머성 화합물.

[0072] 구현예 3: 12 내지 50개의 연결된 뉴클레오사이드로 이루어지고 적어도 8, 적어도 9, 적어도 10, 적어도 11, 적어도 12, 적어도 13, 적어도 14, 적어도 15, 적어도 16, 적어도 17, 적어도 18, 적어도 19, 또는 적어도 20개의 연속적 핵염기의 부분을 포함하는 핵염기 서열을 가지고 있는 변형된 올리고뉴클레오타이드를 포함하는 올리고머성 화합물이며, 상기 부분이 하기에 상보성인, 올리고머성 화합물:

[0073] 서열번호: 2의 핵염기 18,633-18,658의 동일 길이 부분;

[0074] 서열번호: 2의 핵염기 21,721-21,755의 동일 길이 부분;

[0075] 서열번호: 2의 핵염기 27,963-28,016의 동일 길이 부분;

[0076] 서열번호: 2의 핵염기 35,415-35,446의 동일 길이 부분;

[0077] 서열번호: 2의 핵염기 77,221-77,264의 동일 길이 부분;

[0078] 서열번호: 2의 핵염기 81,581-81,612 및/또는 87,838-87,869의 동일 길이 부분;

[0079] 서열번호: 2의 핵염기 81,627-81,651의 동일 길이 부분;

[0080] 서열번호: 2의 핵염기 82,058-82,081의 동일 길이 부분;

[0081] 서열번호: 2의핵염기 82,180-82,220의 동일 길이 부분;

[0082] 서열번호: 2의 핵염기 82,500-82,525의 동일 길이 부분;

[0083] 서열번호: 2의 핵염기 91,038-91,067의 동일 길이 부분;

[0084] 서열번호: 2의 핵염기 92,148-92,173의 동일 길이 부분;

[0085] 서열번호: 2의 핵염기 98,186-98,220의 동일 길이 부분;

[0086] 서열번호: 2의 핵염기 98,218-98,242의 동일 길이 부분;

[0087] 서열번호: 2의 핵염기 99,199-99,223의 동일 길이 부분;

[0088] 서열번호: 2의 핵염기 119,903-119,936의 동일 길이 부분; 또는

[0089] 서열번호: 1의 핵염기 4,062-4,086의 동일 길이 부분.

[0090] 구현예 4. 구현예 1-3 중 어느 하나에 있어서, 변형된 올리고뉴클레오타이드가, 변형된 올리고뉴클레오타이드의 전체 핵염기 서열에 걸쳐서 측정된 경우, 서열번호: 1 또는 서열번호: 2의 핵염기 서열에 적어도 80%, 85%, 90%, 95%, 또는 100% 상보성인 핵염기 서열을 가지고 있는, 올리고머성 화합물.

[0091] 구현예 5. 구현예 1-4 중 어느 하나에 있어서, 변형된 올리고뉴클레오타이드가 적어도 하나의 변형된 뉴클레오사이드를 포함하는, 올리고머성 화합물.

[0092] 구현예 6. 구현예 5에 있어서, 변형된 올리고뉴클레오타이드가 변형된 당 모이어티를 포함하는 적어도 하나의 변형된 뉴클레오사이드를 포함하는, 올리고머성 화합물.

[0093] 구현예 7. 구현예 6에 있어서, 변형된 올리고뉴클레오타이드가 이환형 당 모이어티를 포함하는 적어도 하나의 변형된 뉴클레오사이드를 포함하는, 올리고머성 화합물.

[0094] 구현예 8. 구현예 7에 있어서, 변형된 올리고뉴클레오타이드가 2'-4' 브릿지를 가지고 있는 이환형 당 모이어티를 포함하는 적어도 하나의 변형된 뉴클레오사이드를 포함하며, 상기 2'-4' 브릿지가 -O-CH_2-; 및 -O-$CH(CH_3)$-로부터 선택되는, 올리고머성 화합물.

[0095] 구현예 9. 구현예 5-8 중 어느 하나에 있어서, 변형된 올리고뉴클레오타이드가 비-이환형 변형된 당 모이어티를 포함하는 적어도 하나의 변형된 뉴클레오사이드를 포함하는, 올리고머성 화합물.

[0096] 구현예 10. 구현예 9에 있어서, 변형된 올리고뉴클레오타이드가 2'-MOE 변형된 당 또는 2'-OMe 변형된 당을 포함하는 비-이환형 변형된 당 모이어티를 포함하는 적어도 하나의 변형된 뉴클레오사이드를 포함하는, 올리고머성 화합물.

[0097] 구현예 11. 구현예 5-10 중 어느 하나에 있어서, 변형된 올리고뉴클레오타이드가 당 대리물을 포함하는 적어도 하나의 변형된 뉴클레오사이드를 포함하는, 올리고머성 화합물.

[0098] 구현예 12. 구현예 11에 있어서, 변형된 올리고뉴클레오타이드가 모폴리노 및 PNA로부터 선택된 당 대리물을 포함하는 적어도 하나의 변형된 뉴클레오사이드를 포함하는, 올리고머성 화합물.

[0099] 구현예 13. 구현예 1-12 중 어느 하나에 있어서, 변형된 올리고뉴클레오타이드가 하기를 포함하는 당 모티프를 가지며:

[0100] 1-5개의 연결된 5'-영역 뉴클레오사이드로 이루어지는 5'-영역;

[0101] 6-10개의 연결된 중심 영역 뉴클레오사이드로 이루어지는 중심 영역; 및

[0102] 1-5개의 연결된 3'-영역 뉴클레오사이드로 이루어지는 3'-영역;

[0103] 각각의 상기 5'-영역 뉴클레오사이드 및 각각의 상기 3'-영역 뉴클레오사이드가 변형된 당 모이어티를 포함하고 각각의 상기 중심 영역 뉴클레오사이드가 미변형된 2'-데옥시리보실 당 모이어티를 포함하는, 올리고머성 화합물.

[0104] 구현예 14. 구현예 1-13 중 어느 하나에 있어서, 변형된 올리고뉴클레오타이드가 적어도 하나의 변형된 인터뉴클레오사이드 연결기를 포함하는, 올리고머성 화합물.

[0105] 구현예 15. 구현예 14에 있어서, 변형된 올리고뉴클레오타이드의 각 인터뉴클레오사이드 연결기가 변형된 인터뉴클레오사이드 연결기인, 올리고머성 화합물.

[0106] 구현예 16. 구현예 14 또는 15에 있어서, 적어도 하나의 인터뉴클레오사이드 연결기가 포스포로티오에이트 인터뉴클레오사이드 연결기인, 올리고머성 화합물.

[0107] 구현예 17. 구현예 14 또는 16에 있어서, 변형된 올리고뉴클레오타이드가 적어도 하나의 포스포디에스테르 인터뉴클레오사이드 연결기를 포함하는, 올리고머성 화합물.

[0108] 구현예 18. 구현예 14, 16, 또는 17 중 어느 하나에 있어서, 각 인터뉴클레오사이드 연결기가 포스포디에스테르 인터뉴클레오사이드 연결기 또는 포스포로티오에이트 인터뉴클레오사이드 연결기인, 올리고머성 화합물.

[0109] 구현예 19. 구현예 1-18 중 어느 하나에 있어서, 변형된 올리고뉴클레오타이드가 적어도 하나의 변형된 핵염기를 포함하는, 올리고머성 화합물.

[0110] 구현예 20. 구현예 19에 있어서, 변형된 핵염기가 5-메틸 시토신인, 올리고머성 화합물.

[0111] 구현예 21. 구현예 1-20 중 어느 하나에 있어서, 변형된 올리고뉴클레오타이드가 12-30, 12-22, 12-20, 14-20, 15-25, 16-20, 18-22 또는 18-20개의 연결된 뉴클레오사이드로 이루어지는, 올리고머성 화합물.

[0112] 구현예 22. 구현예 1-21 중 어느 하나에 있어서, 변형된 올리고뉴클레오타이드가 17 또는 20개의 연결된 뉴클레오사이드로 이루어지는, 올리고머성 화합물.

[0113] 구현예 23. 구현예 1-22 중 어느 하나에 있어서, 변형된 올리고뉴클레오타이드로 이루어지는 올리고머성 화합물.

[0114] 구현예 24. 구현예 1-22 중 어느 하나에 있어서, 컨쥬게이트 모이어티 및 컨쥬게이트 링커를 포함하는 컨쥬게이트 그룹을 포함하는 올리고머성 화합물.

[0115] 구현예 25. 구현예 24에 있어서, 컨쥬게이트 그룹이 1-3개의 GalNAc 리간드를 포함하는 GalNAc 클러스터를 포함하는, 올리고머성 화합물.

[0116] 구현예 26. 구현예 24 또는 25에 있어서, 컨쥬게이트 링커가 단일 결합으로 이루어지는, 올리고머성 화합물.

[0117] 구현예 27. 구현예 25에 있어서, 컨쥬게이트 링커가 절단가능한, 올리고머성 화합물.

[0118] 구현예 28. 구현예 27에 있어서, 컨쥬게이트 링커가 1-3개의 링커-뉴클레오사이드를 포함하는, 올리고머성 화합물.

[0119] 구현예 29. 구현예 24-28 중 어느 하나에 있어서, 컨쥬게이트 그룹이 변형된 올리고뉴클레오타이드의 5'-말단에서 변형된 올리고뉴클레오타이드에 부착되는, 올리고머성 화합물.

[0120] 구현예 30. 구현예 24-28 중 어느 하나에 있어서, 컨쥬게이트 그룹이 변형된 올리고뉴클레오타이드의 3'-말단에서 변형된 올리고뉴클레오타이드에 부착되는, 올리고머성 화합물.

[0121] 구현예 31. 구현예 1-30 중 어느 하나에 있어서, 말단기를 포함하는 올리고머성 화합물.

[0122] 구현예 32. 구현예 1-31 중 어느 하나에 있어서, 단일가닥 올리고머성 화합물인 올리고머성 화합물.

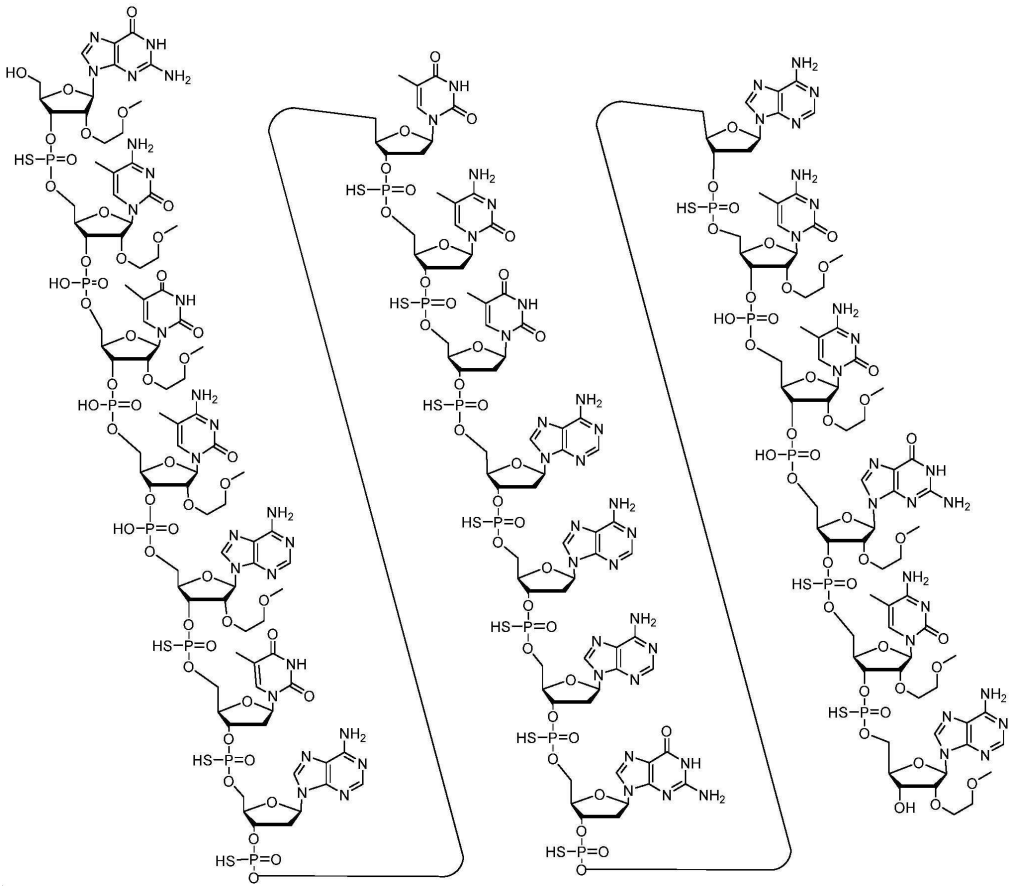
[0123] 구현예 33. 구현예 1-27 또는 29-31 중 어느 하나에 있어서, 링커-뉴클레오사이드를 포함하지 않는 올리고머성 화합물.

[0124] 구현예 34. 구현예 1-31 또는 33 중 어느 하나에 따른 올리고머성 화합물을 포함하는 올리고머성 듀플렉스.

[0125] 구현예 35. 구현예 1-33 중 어느 하나에 따른 올리고머성 화합물 또는 구현예 34에 따른 올리고머성 듀플렉스를 포함하거나 또는 이로 이루어지는 안티센스 화합물.

[0126] 구현예 36. 구현예 1-33 중 어느 하나에 따른 올리고머성 화합물 또는 구현예 34에 따른 올리고머성 듀플렉스, 및 약제학적으로 허용가능한 담체 또는 희석제를 포함하는 약제학적 조성물.

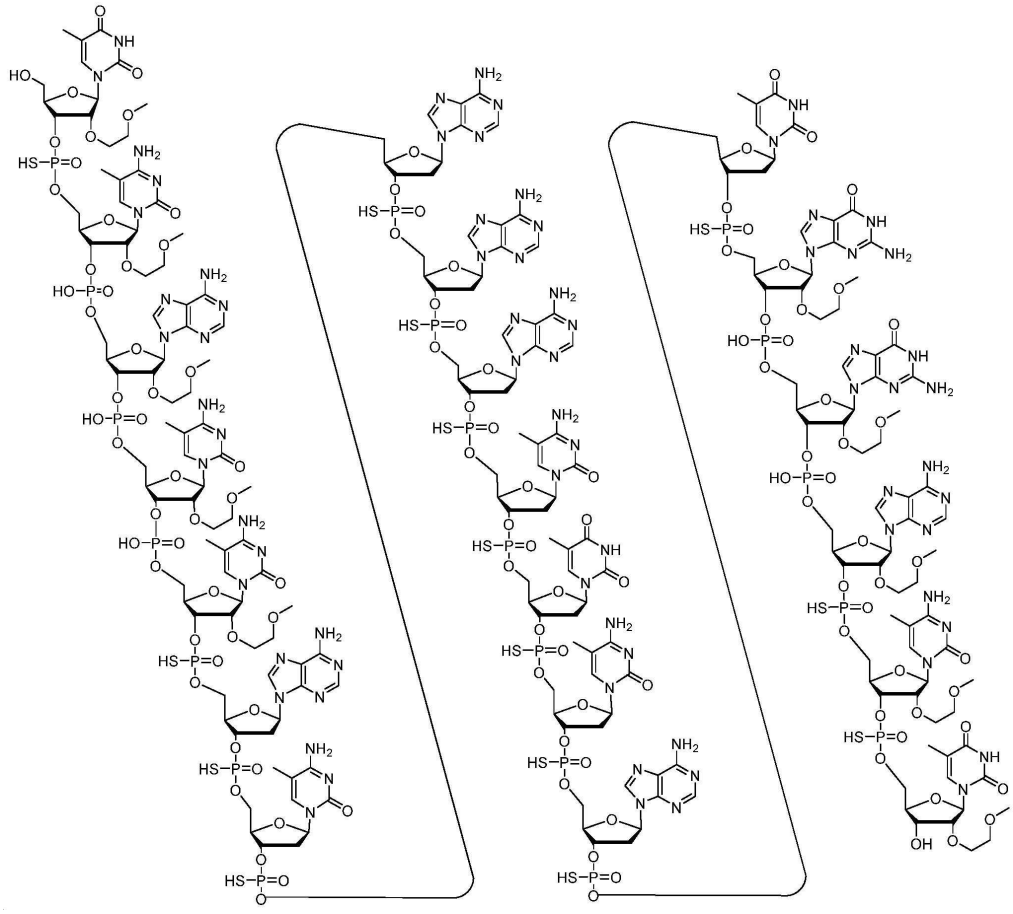
[0127] 구현예 37. 하기 식에 따른 변형된 올리고뉴클레오타이드:

[0128] 

[0129] (서열번호: 222)

[0130] 또는 이의 염.

[0131] 구현예 38. 하기 식에 따른 변형된 올리고뉴클레오타이드:

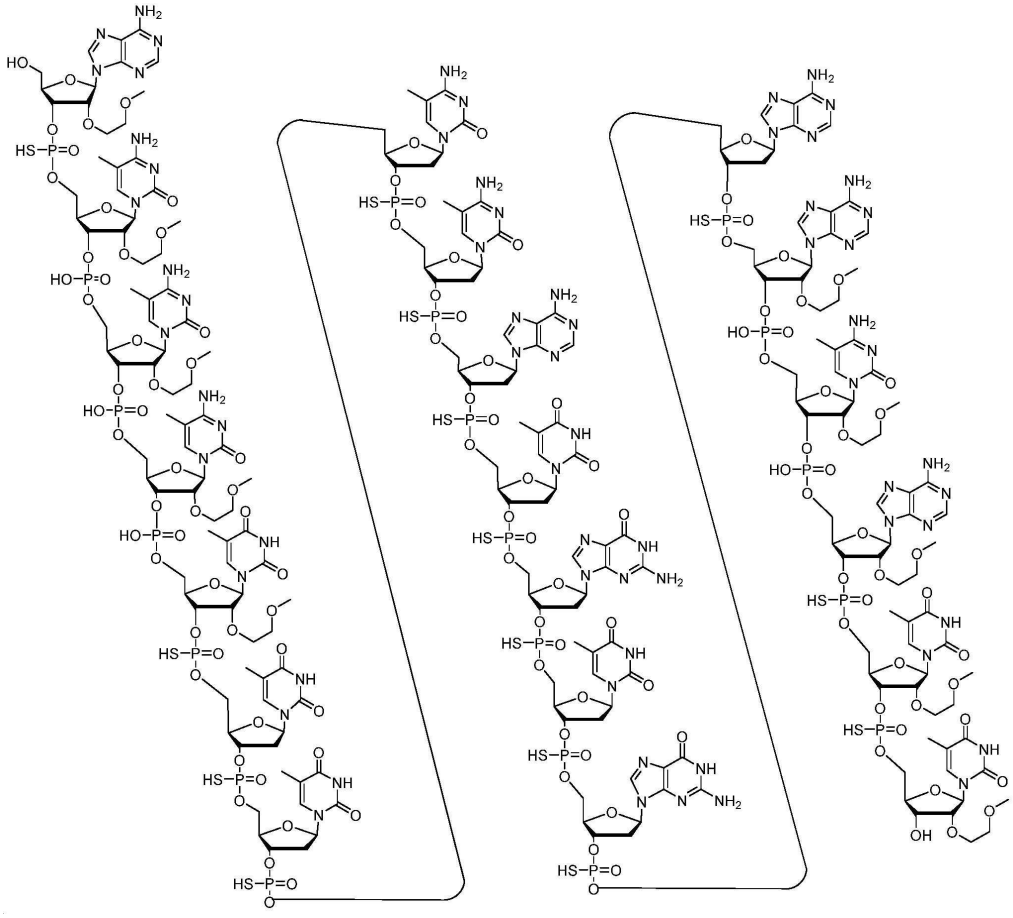


[0132]

[0133] (서열번호: 888)

[0134] 또는 이의 염.

[0135] 구현예 39. 하기 식에 따른 변형된 올리고뉴클레오타이드:

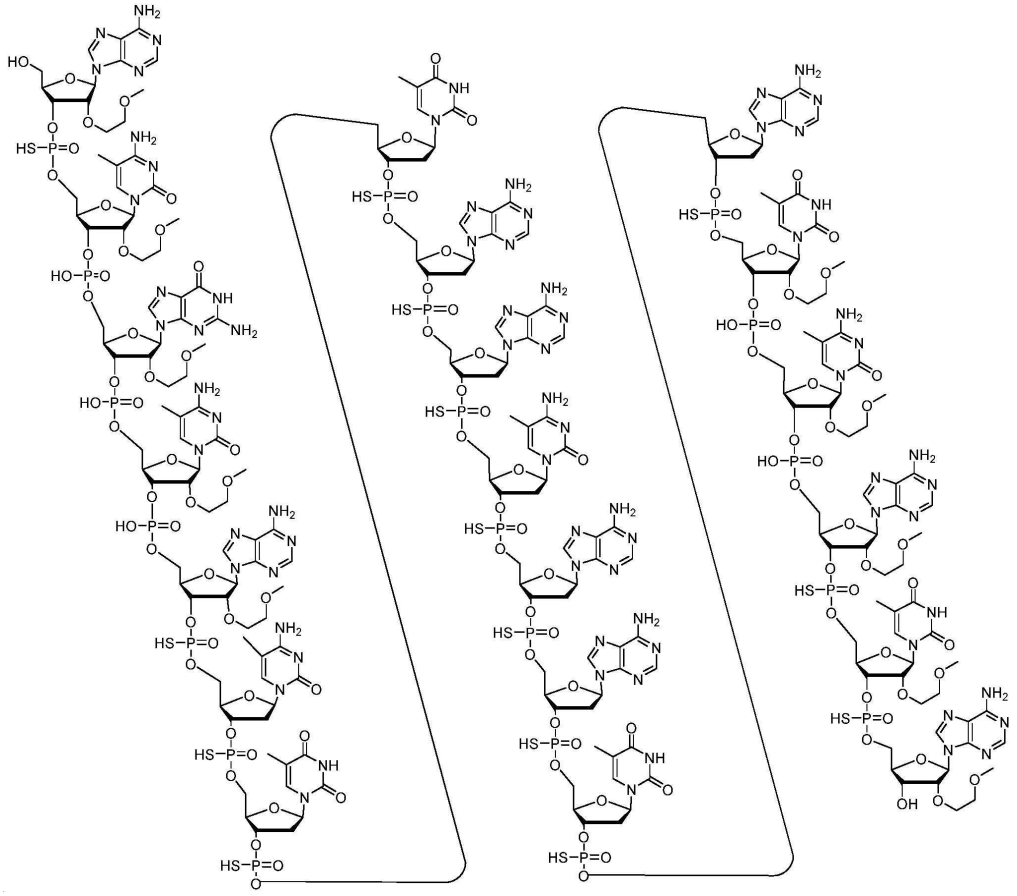


[0136]

[0137] (서열번호: 1431)

[0138] 또는 이의 염.

[0139] 구현예 40. 하기 식에 따른 변형된 올리고뉴클레오타이드:

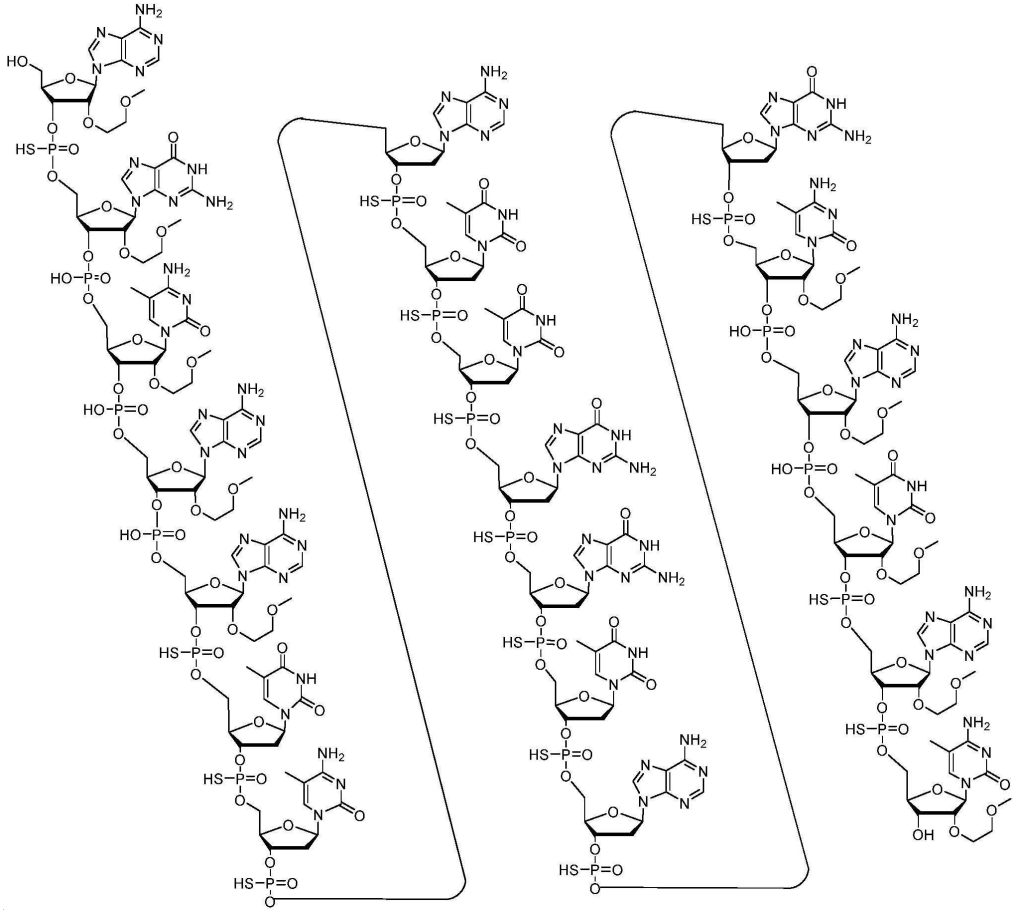


[0140]

[0141] (서열번호: 3590)

[0142] 또는 이의 염.

[0143] 구현예 41. 하기 식에 따른 변형된 올리고뉴클레오타이드:

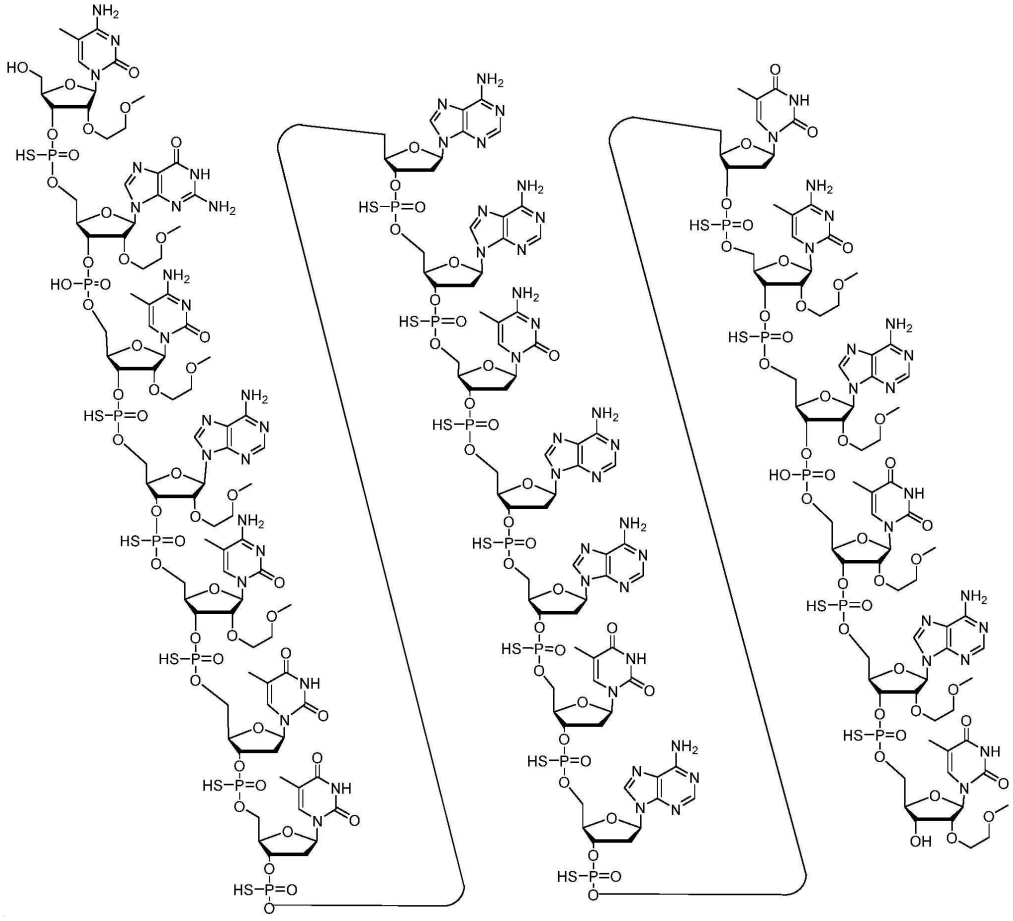


[0144]

[0145] (서열번호: 3385)

[0146] 또는 이의 염.

[0147] 구현예 42. 하기 식에 따른 변형된 올리고뉴클레오타이드:



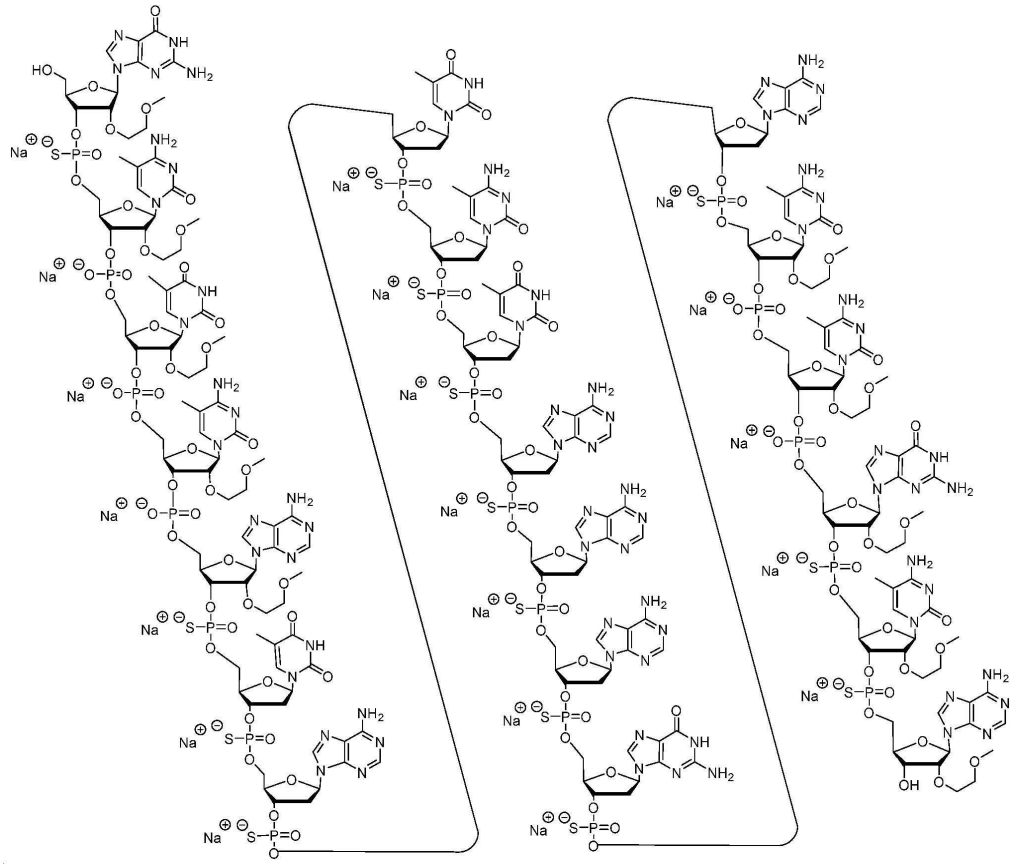
[0148]

[0149] (서열번호: 852)

[0150] 또는 이의 염.

[0151] 구현예 43. 구현예 37-42 중 어느 하나에 있어서, 상기 식의 나트륨염인, 변형된 올리고뉴클레오타이드.

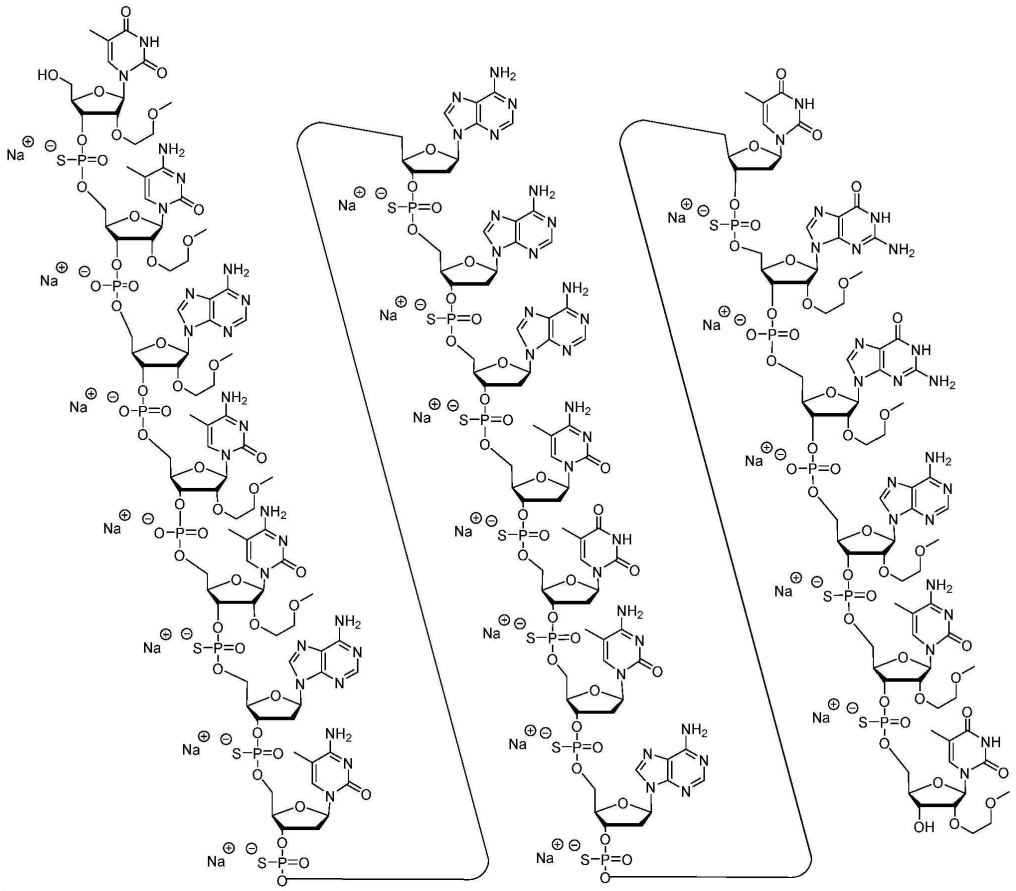
[0152] 구현예 44. 하기 식에 따른 변형된 올리고뉴클레오타이드:



[0153]

[0154] (서열번호: 222).

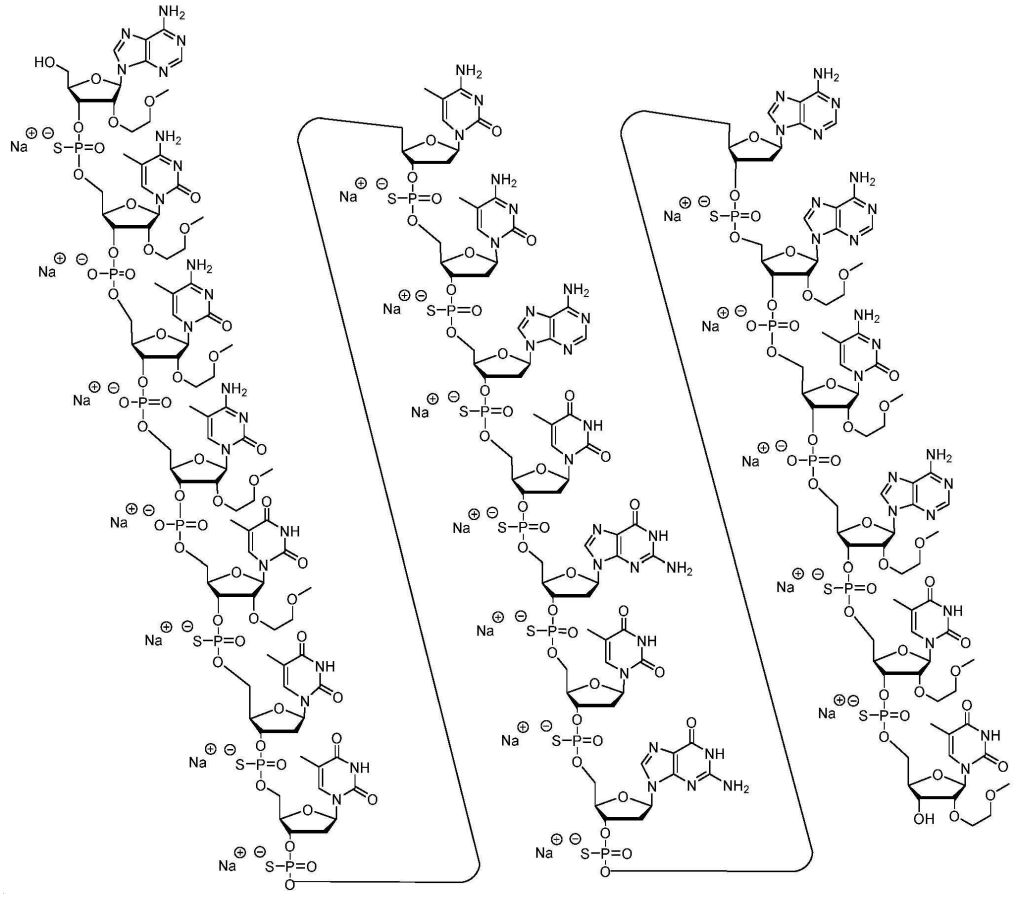
[0155] 구현예 45. 하기 식에 따른 변형된 올리고뉴클레오타이드:



[0156]

[0157] (서열번호: 888).

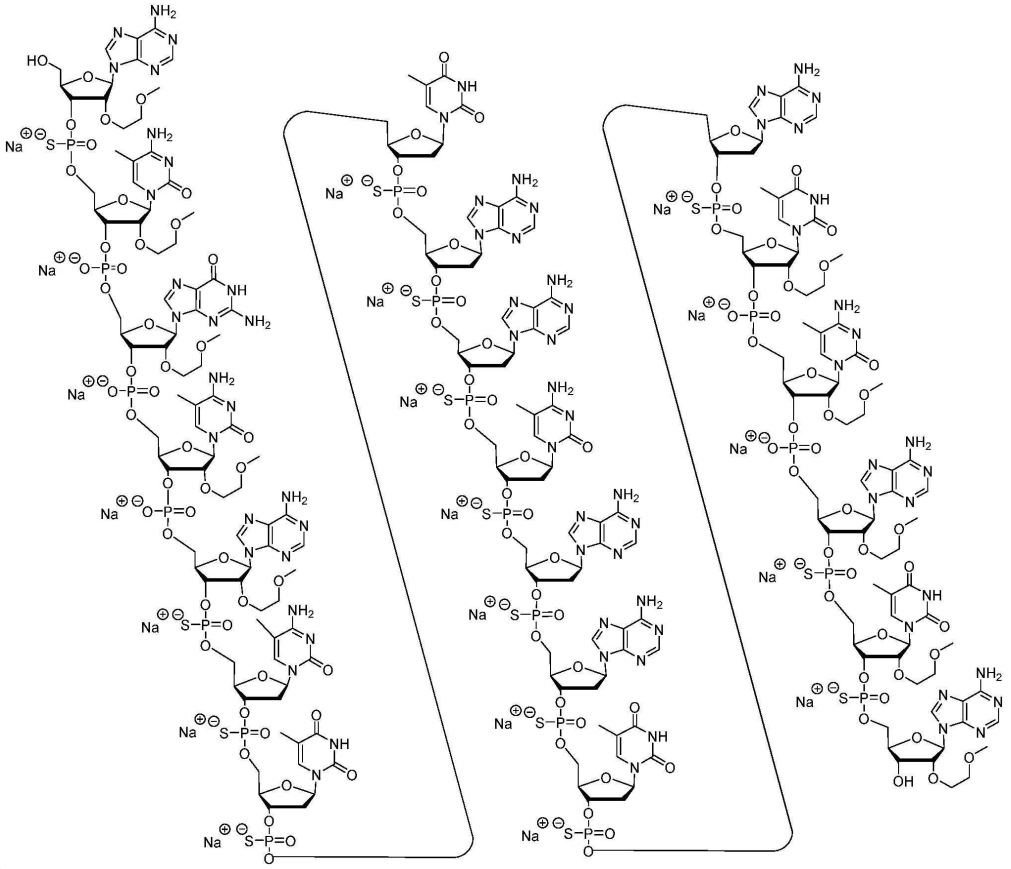
[0158] 구현예 46. 하기 식에 따른 변형된 올리고뉴클레오타이드:



[0159]

[0160] (서열번호: 1431).

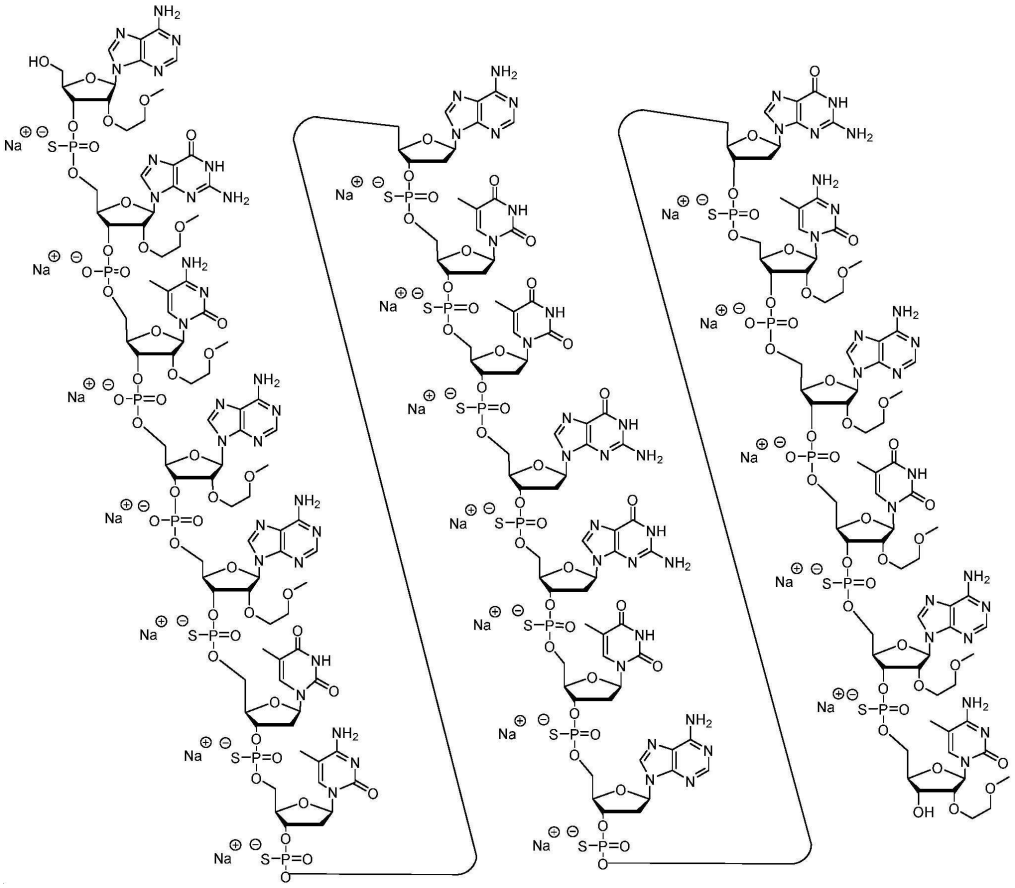
[0161] 구현예 47. 하기 식에 따른 변형된 올리고뉴클레오타이드:



[0162]

[0163] (서열번호: 3590).

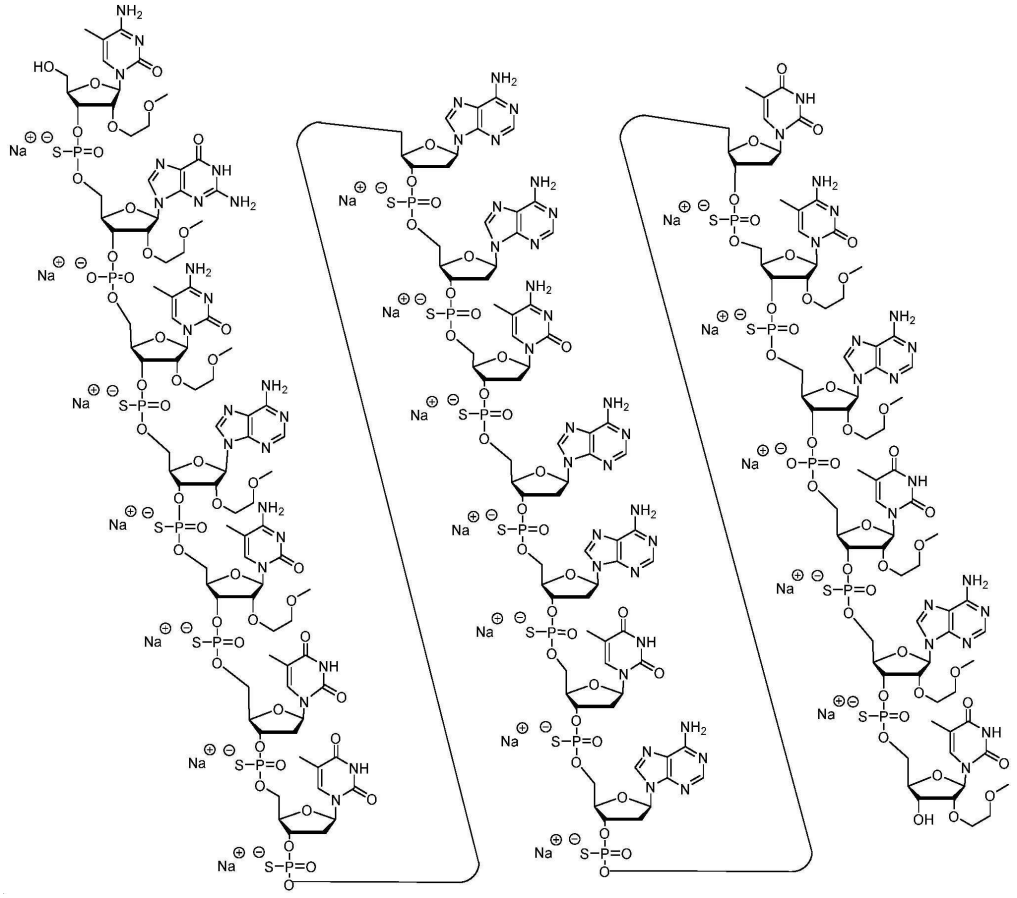
[0164] 구현예 48. 하기 식에 따른 변형된 올리고뉴클레오타이드:



[0165]

[0166] (서열번호: 3385).

[0167] 구현예 49. 하기 식에 따른 변형된 올리고뉴클레오타이드:



[0168]

[0169] (서열번호: 852).

[0170] 구현예 50. 구현예 37-49 중 어느 하나에 따른 변형된 올리고뉴클레오타이드의 키랄 풍부 집단이며, 특정 입체화학적 배치형태를 가지고 있는 적어도 하나의 특정 포스포로티오에이트 인터뉴클레오사이드 연결기를 포함하는 변형된 올리고뉴클레오타이드가 풍부한 키랄 풍부 집단.

[0171] 구현예 51. 구현예 50에 있어서, (Sp) 배치형태를 가지고 있는 적어도 하나의 특정 포스포로티오에이트 인터뉴클레오사이드 연결기를 포함하는 변형된 올리고뉴클레오타이드가 풍부한 키랄 풍부 집단.

[0172] 구현예 52. 구현예 50 또는 51에 있어서, (Rp) 배치형태를 가지고 있는 적어도 하나의 특정 포스포로티오에이트 인터뉴클레오사이드 연결기를 가지고 있는 변형된 올리고뉴클레오타이드가 풍부한 키랄 풍부 집단.

[0173] 구현예 53. 구현예 50에 있어서, 각 포스포로티오에이트 인터뉴클레오사이드 연결기에서 특정, 독립적으로 선택된 입체화학적 배치형태를 가지고 있는 변형된 올리고뉴클레오타이드가 풍부한 키랄 풍부 집단.

[0174] 구현예 54. 구현예 53에 있어서, 각 포스포로티오에이트 인터뉴클레오사이드 연결기에서 (Sp) 배치형태를 가지고 있는 변형된 올리고뉴클레오타이드가 풍부한 키랄 풍부 집단.

[0175] 구현예 55. 구현예 53에 있어서, 각 포스포로티오에이트 인터뉴클레오사이드 연결기에서 (Rp) 배치형태를 가지고 있는 변형된 올리고뉴클레오타이드가 풍부한 키랄 풍부 집단.

[0176] 구현예 56. 구현예 50 또는 구현예 53에 있어서, 5'에서 3' 방향으로, *Sp*-*Sp*-*Rp* 배치형태의 적어도 3개의 연속적 포스포로티오에이트 인터뉴클레오사이드 연결기를 가지고 있는 변형된 올리고뉴클레오타이드가 풍부한 키랄 풍부 집단.

[0177] 구현예 57. 구현예 37-49 중 어느 하나에 따른 변형된 올리고뉴클레오타이드의 집단이며, 변형된 올리고뉴클레오타이드의 포스포로티오에이트 인터뉴클레오사이드 연결기의 모두가 스테레오랜덤인, 집단.

[0178] 구현예 58. 구현예 37-49 중 어느 하나에 따른 변형된 올리고뉴클레오타이드 및 약제학적으로 허용가능한 희석제 또는 담체를 포함하는 약제학적 조성물.

[0179] 구현예 59. 구현예 58에 있어서, 약제학적으로 허용가능한 희석제가 인공 뇌척수액인, 약제학적 조성물.

[0180] 구현예 60. 구현예 59에 있어서, 변형된 올리고뉴클레오타이드 및 인공 뇌척수액으로 본질적으로 이루어지는 약제학적 조성물.

[0181] 구현예 61. 구현예 36 또는 58 내지 60 중 어느 하나에 따른 약제학적 조성물을 동물에 투여하는 단계를 포함하는 방법.

[0182] 구현예 62. 구현예 36 또는 58 내지 60 중 어느 하나에 따른 약제학적 조성물의 치료적 유효량을 LRRK2와 연관된 질환을 가지고 있거나 발병의 위험에 처한 개체에 투여하는 단계; 및 그것에 의해 LRRK2와 연관된 질환을 치료하는 단계를 포함하는, LRRK2와 연관된 질환의 치료 방법.

[0183] 구현예 63. 구현예 62에 있어서, LRRK2와 연관된 질환이 신경퇴행성 질환인, 방법.

[0184] 구현예 64. 구현예 63에 있어서, 신경퇴행성 질환이 파킨슨병인, 방법.

[0185] 구현예 65. 구현예 64에 있어서, 신경퇴행성 질환의 적어도 하나의 징후 또는 특징이 개선되는, 방법.

[0186] 구현예 66. 구현예 65에 있어서, 징후 또는 특징이 운동실조증, 신경병증, 및 응집체 형성 중 임의의 것인 방법.

[0187] 구현예 67. 하기 식에 따른 변형된 올리고뉴클레오타이드를 포함하는 올리고머성 화합물: Ges mCeo Teo mCeo Aes Tds Ads Tds mCds Tds Ads Ads Ads Gds Ads mCeo mCeo Ges mCes Ae (서열번호: 222); 여기서,

[0188] A = 아데닌 핵염기,

[0189] mC = 5-메틸 시토신 핵염기,

[0190] G = 구아닌 핵염기,

[0191] T = 티민 핵염기,

[0192] e = 2'-MOE 변형된 당,

[0193] d = 2'-데옥시리보오스 당,

[0194] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

[0195] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

[0196] 구현예 68. 하기 식에 따른 변형된 올리고뉴클레오타이드를 포함하는 올리고머성 화합물: Tes mCeo Aeo mCeo mCes Ads mCds Ads Ads Ads mCds Tds mCds Ads Tds Geo Geo Aes mCes Te (서열번호: 888); 여기서,

[0197] A = 아데닌 핵염기,

[0198] mC = 5-메틸 시토신 핵염기,

[0199] G = 구아닌 핵염기,

[0200] T = 티민 핵염기,

[0201] e = 2'-MOE 변형된 당,

[0202] d = 2'-데옥시리보오스 당,

[0203] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

[0204] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

[0205] 구현예 69. 하기 식에 따른 변형된 올리고뉴클레오타이드를 포함하는 올리고머성 화합물: Aes mCeo mCeo mCeo Tes Tds Tds mCds mCds Ads Tds Gds Tds Gds Ads Aeo mCeo Aes Tes Te (서열번호: 1431); 여기서,

[0206] A = 아데닌 핵염기,

[0207] mC = 5-메틸 시토신 핵염기,

[0208] G = 구아닌 핵염기,

[0209] T = 티민 핵염기,

[0210] e = 2'-MOE 변형된 당,

[0211] d = 2'-데옥시리보오스 당,

[0212] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

[0213] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

[0214] 구현예 70. 하기 식에 따른 변형된 올리고뉴클레오타이드를 포함하는 올리고머성 화합물: Aes mCeo Geo mCeo Aes mCds Tds Tds Ads Ads mCds Ads Ads Tds Ads Teo mCeo Aes Tes Ae (서열번호: 3590); 여기서,

[0215] A = 아데닌 핵염기,

[0216] mC = 5-메틸 시토신 핵염기,

[0217] G = 구아닌 핵염기,

[0218] T = 티민 핵염기,

[0219] e = 2'-MOE 변형된 당,

[0220] d = 2'-데옥시리보오스 당,

[0221] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

[0222] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

[0223] 구현예 71. 하기 식에 따른 변형된 올리고뉴클레오타이드를 포함하는 올리고머성 화합물: Aes Geo mCeo Aeo Aes Tds mCds Ads Tds Tds Gds Gds Tds Ads Gds mCeo Aeo Tes Aes mCe (서열번호: 3385); 여기서,

[0224] A = 아데닌 핵염기,

[0225] mC = 5-메틸 시토신 핵염기,

[0226] G = 구아닌 핵염기,

[0227] T = 티민 핵염기,

[0228] e = 2'-MOE 변형된 당,

[0229] d = 2'-데옥시리보오스 당,

[0230] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

[0231] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

[0232] 구현예 72. 하기 식에 따른 변형된 올리고뉴클레오타이드를 포함하는 올리고머성 화합물: mCes Geo mCes Aes mCes Tds Tds Ads Ads mCds Ads Ads Tds Ads Tds mCes Aeo Tes Aes Te (서열번호: 852); 여기서,

[0233] A = 아데닌 핵염기,

[0234] mC = 5-메틸 시토신 핵염기,

[0235] G = 구아닌 핵염기,

[0236] T = 티민 핵염기,

[0237] e = 2'-MOE 변형된 당,

[0238] d = 2'-데옥시리보오스 당,

[0239] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

[0240] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

[0241] 구현예 73. 구현예 3에 있어서, 변형된 올리고뉴클레오타이드가 RNAi 화합물인, 올리고머성 화합물.

[0242] 구현예 74. 구현예 73 항에 있어서, RNAi 화합물이 ssRNA 또는 siRNA인, 올리고머성 화합물.

[0243] I. 특정 올리고뉴클레오타이드

[0244] 특정 구현예에서, 연결된 뉴클레오사이드로 이루어지는, 올리고뉴클레오타이드를 포함하는 올리고머성 화합물은 본 명세서에 제공된다. 올리고뉴클레오타이드는 미변형된 올리고뉴클레오타이드 (RNA 또는 DNA)일 수 있거나 변형된 올리고뉴클레오타이드일 수 있다. 변형된 올리고뉴클레오타이드는 미변형된 RNA 또는 DNA에 비하여 적어도 하나의 변형을 포함한다. 즉, 변형된 올리고뉴클레오타이드는 (변형된 당 모이어티 및/또는 변형된 핵염기를 포함하는) 적어도 하나의 변형된 뉴클레오사이드 및/또는 적어도 하나의 변형된 인터뉴클레오사이드 연결기를 포함한다.

[0245] A. 특정 변형된 뉴클레오사이드

[0246] 변형된 뉴클레오사이드는 변형된 당 모이어티 또는 변형된 핵염기 또는 당 모이어티 및 변형된 핵염기 둘 모두를 포함한다.

[0247] 1. 특정 당 모이어티

[0248] 특정 구현예에서, 변형된 당 모이어티는 비-이환형 변형된 당 모이어티이다. 특정 구현예에서, 변형된 당 모이어티는 이환형 또는 삼환형 당 모이어티이다. 특정 구현예에서, 변형된 당 모이어티는 당 대리물이다. 그와 같은 당 대리물은 변형된 당 모이어티의 다른 유형의 것에 상응하는 하나 이상의 치환을 포함할 수 있다.

[0249] 특정 구현예에서, 변형된 당 모이어티는 이환형 구조를 형성하기 위해 푸라노실 고리의 2개의 원자를 브릿징하지 않는 하나 이상의 치환기를 가진 푸라노실 고리를 포함하는 비-이환형 변형된 당 모이어티이다. 그와 같은 비 브릿징 치환체는, 비제한적으로 2', 4', 및/또는 5' 위치에서 치환체를 포함하는, 푸라노실의 임의의 위치에 있을 수 있다. 특정 구현예에서 비-이환형 변형된 당 모이어티의 하나 이상의 비-브릿징 치환체는 분지형이다. 비-이환형 변형된 당 모이어티에 적당한 2'-치환기의 예는 하기를 비제한적으로 포함한다: 2'-F, 2'-OCH_3 ("OMe" 또는 "O-메틸"), 및 2'-$O(CH_2)_2OCH_3$ ("MOE"). 특정 구현예에서, 2'-치환기는 하기중으로부터 선택된다: 할로, 알릴, 아미노, 아지도, SH, CN, OCN, CF_3, OCF_3, O-C_1-C_{10} 알콕시, O-C_1-C_{10} 치환된 알콕시, O-C_1-C_{10} 알킬, O-C_1-C_{10} 치환된 알킬, S-알킬, $N(R_m)$-알킬, O-알케닐, S-알케닐, $N(R_m)$-알케닐, O-알키닐, S-알키닐, $N(R_m)$-알키닐, O-알킬레닐-O-알킬, 알키닐, 알크아릴, 아르알킬, O-알크아릴, O-아르알킬, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$ 또는 $OCH_2C(=O)-N(R_m)(R_n)$, 여기에서 각 R_m 및 R_n은, 독립적으로, Cook 등, U.S. 6,531,584; Cook 등, U.S. 5,859,221; 및 Cook 등, U.S. 6,005,087에서 기재된 H, 아미노 보호기, 또는 치환된 또는 미치환된 C_1-C_{10} 알킬, 및 2'-치환기임. 이들 2'-치환기의 특정 구현예는 독립적으로 하기중으로부터 선택된 하나 이상의 치환기로 추가로 치환될 수 있다: 하이드록실, 아미노, 알콕시, 카복시, 벤질, 페닐, 니트로 (NO2), 티올, 티오알콕시, 티오알킬, 할로겐, 알킬, 아릴, 알케닐 및 알키닐. 비-이환형 변형된 당 모이어티에 적당한 4'-치환기의 예는 비제한적으로 알콕시 (예를 들면, 메톡시), 알킬, 및 Manoharan 등, WO 2015/106128에서 기재된 것을 포함한다. 비-이환형 변형된 당 모이어티에 적당한 5'-치환기의 예는 하기를 비제한적으로 포함한다: 5-메틸 (R 또는 S), 5'-비닐, 및 5'-메톡시. 특정 구현예에서, 비-이환형 변형된 당 모이어티는 1개 초과 비-브릿징 당 치환체, 예를 들어, 2'-F-5'-메틸 당 모이어티 및 변형된 당 모이어티 그리고 Migawa 등, WO 2008/101157 및 Rajeev 등, US2013/0203836에서 기재된 변형된 뉴클레오사이드를 포함한다.).

[0250] 특정 구현예에서, 2'-치환된 비-이환형 변형된 뉴클레오사이드는 하기로부터 선택된 비-브릿징 2'-치환기를 포함하는 당 모이어티를 포함한다: F, NH_2, N_3, OCF_3, OCH_3, $O(CH_2)_3NH_2$, $CH_2CH=CH_2$, $OCH_2CH=CH_2$, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(R_m)(R_n)$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, 및 N-치환된 아세트아미드 ($OCH_2C(=O)-N(R_m)(R_n)$), 여기에서 각 R_m 및 R_n은, 독립적으로, H, 아미노 보호기, 또는 치환된 또는 미치환된 C_1-C_{10} 알킬임.

[0251] 특정 구현예에서, 2'-치환된 뉴클레오사이드 비-이환형 변형된 뉴클레오사이드는 하기로부터 선택된 비-브릿징 2'-치환기를 포함하는 당 모이어티를 포함한다: F, OCF_3, OCH_3, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2ON(CH_3)_2$, $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, 및 $OCH_2C(=O)-N(H)CH_3$ ("NMA").

[0252] 특정 구현예에서, 2'-치환된 뉴클레오사이드 비-이환형 변형된 뉴클레오사이드는 하기로부터 선택된 비-브릿징 2'-치환기를 포함하는 당 모이어티를 포함한다: F, OCH_3, 및 $OCH_2CH_2OCH_3$.

[0253] 특정 모디페드 당 모이어티는, 이환형 당 모이어티를 초래하는, 제2 고리를 형성하기 위해 푸라노실 고리의 2개의 원자를 브릿징하는 치환체를 포함한다. 특정 상기 구현예에서, 이환형 당 모이어티는 4' 및 2' 푸라노스 고리 원자 사이 브릿지를 포함한다. 그와 같은 4' 내지 2' 브릿징 당 치환체의 예는 하기를 비제한적으로 포함한다: 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2' ("LNA"), 4'-CH_2-S-2', 4'-$(CH_2)_2$-O-2' ("ENA"), 4'-$CH(CH_3)$-O-2' ("구속된 에틸" 또는 "cEt"로 칭함), 4'-CH_2-O-CH_2-2', 4'-CH_2-N(R)-2', 4'-$CH(CH_2OCH_3)$-O-2' ("구속된 MOE" 또는 "cMOE") 및 이의 유사체 (참고, 예를 들면, Seth 등, U.S. 7,399,845, Bhat 등, U.S. 7,569,686, Swayze 등, U.S. 7,741,457, 및 Swayze 등, U.S. 8,022,193), 4'-$C(CH_3)(CH_3)$-O-2' 및 이의 유사체 (참고, 예를 들면, Seth 등, U.S. 8,278,283), 4'-CH_2-$N(OCH_3)$-2' 및 이의 유사체 (참고, 예를 들면, Prakash 등, U.S. 8,278,425), 4'-CH_2-O-$N(CH_3)$-2' (참고, 예를 들면, Allerson 등, U.S. 7,696,345 및 Allerson 등, U.S. 8,124,745), 4'-CH_2-$C(H)(CH_3)$-2' (참고, 예를 들면, Zhou, 등, *J. Org.Chem.*, 2009, 74, 118-134), 4'-CH_2-$C(=CH_2)$-2' 및 이의 유사체 (참고 예를 들면, Seth 등, U.S. 8,278,426), 4'-$C(R_aR_b)$-N(R)-O-2', 4'-$C(R_aR_b)$-O-N(R)-2', 4'-CH_2-O-N(R)-2', 및 4'-CH_2-N(R)-O-2', 상기 각 R, R_a, 및 R_b는, 독립적으로, H, 보호기, 또는 C_1-C_{12} 알킬임 (참고, 예를 들어 Imanishi 등, U.S. 7,427,672).

[0254] 특정 구현예에서, 그와 같은 4' 내지 2' 브릿지는 독립적으로 하기로부터 독립적으로 선택된 1 내지 4개의 연결된 기를 포함한다: -$[C(R_a)(R_b)]_n$-, -$[C(R_a)(R_b)]_n$-O-, -$C(R_a)$=$C(R_b)$-, -$C(R_a)$=N-, -C(=NR_a)-, -C(=O)-, -C(=S)-, -O-, -$Si(R_a)_2$-, -$S(=O)_x$-, 및 -N(R_a)-;

[0255] 여기서:

[0256] x는 0, 1, 또는 2이고;

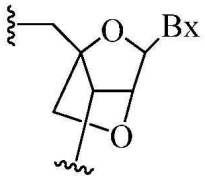
[0257] n은 1, 2, 3, 또는 4이고;

[0258] 각 R_a 및 R_b는, 독립적으로, H, 보호기, 하이드록실, C_1-C_{12} 알킬, 치환된 C_1-C_{12} 알킬, C_2-C_{12} 알케닐, 치환된 C_2-C_{12} 알케닐, C_2-C_{12} 알키닐, 치환된 C_2-C_{12} 알키닐, C_5-C_{20} 아릴, 치환된 C_5-C_{20} 아릴, 복소환 라디칼, 치환된 복소환 라디칼, 헤테로아릴, 치환된 헤테로아릴, C_5-C_7 지환족 라디칼, 치환된 C_5-C_7 지환족 라디칼, 할로겐, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, 아실 (C(=O)-H), 치환된 아실, CN, 설포닐 ($S(=O)_2$-J_1), 또는 설폭실 (S(=O)-J_1)이고;

[0259] 각 J_1 및 J_2는, 독립적으로, H, C_1-C_{12} 알킬, 치환된 C_1-C_{12} 알킬, C_2-C_{12} 알케닐, 치환된 C_2-C_{12} 알케닐, C_2-C_{12} 알키닐, 치환된 C_2-C_{12} 알키닐, C_5-C_{20} 아릴, 치환된 C_5-C_{20} 아릴, 아실 (C(=O)-H), 치환된 아실, 복소환 라디칼, 치환된 복소환 라디칼, C_1-C_{12} 아미노알킬, 치환된 C_1-C_{12} 아미노알킬, 또는 보호기임.

[0260] 추가의 이환형 당 모이어티는 당해 기술에 공지되어 있다, 참고, 예를 들어: Freier 등, *Nucleic Acids Research*, 1997, 25(22), 4429-4443, Albaek 등, *J. Org. Chem.*, 2006, 71, 7731-7740, Singh 등, *Chem. Commun.*, 1998, 4, 455-456; Koshkin 등, *Tetrahedron*, 1998, 54, 3607-3630; Kumar 등, *Bioorg. Med. Chem. Lett.*, 1998, 8, 2219-2222; Singh 등, *J. Org. Chem.*, 1998, 63, 10035-10039; Srivastava 등, *J. Am. Chem. Soc.*, 20017, 129, 8362-8379; Wengel et a., U.S. 7,053,207; Imanishi 등, U.S. 6,268,490; Imanishi 등. U.S. 6,770,748; Imanishi 등, U.S.RE44,779; Wengel 등, U.S. 6,794,499; Wengel 등, U.S. 6,670,461; Wengel 등, U.S. 7,034,133; Wengel 등, U.S. 8,080,644; Wengel 등, U.S. 8,034,909; Wengel 등, U.S. 8,153,365; Wengel 등, U.S. 7,572,582; 및 Ramasamy 등, U.S. 6,525,191;; Torsten 등, WO 2004/106356; Wengel 등, WO 1999/014226; Seth 등, WO 2007/134181; Seth 등, U.S. 7,547,684; Seth 등, U.S. 7,666,854; Seth 등, U.S. 8,088,746; Seth 등, U.S. 7,750,131; Seth 등, U.S. 8,030,467; Seth 등, U.S. 8,268,980; Seth 등, U.S. 8,546,556; Seth 등, U.S. 8,530,640; Migawa 등, U.S. 9,012,421; Seth 등, U.S. 8,501,805; 및 미국 특허 공보 번호 Allerson 등, US2008/0039618 및 Migawa 등, US2015/0191727.

[0261] 특정 구현예에서, 이환형 당 모이어티 그리고 그와 같은 이환형 당 모이어티를 편입시키는 뉴클레오사이드는 추가로 이성질체 배치형태에 의해 정의된다. 예를 들어, (본 명세서에 기재된) LNA 뉴클레오사이드는 α-L 배치형태 또는 β-D 배치형태일 수 있다.

[0262] 



[0263] LNA (β-D-배치형태) α-*L*-LNA (α-*L*-배치형태)

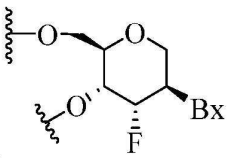
[0264] 브릿지 = 4'-CH_2-O-2' 브릿지 = 4'-CH_2-O-2'

[0265] α-L-메틸렌옥시 (4'-CH_2-O-2') 또는 α-L-LNA 이환형 뉴클레오사이드는 안티센스 활성을 보여주었던 올리고뉴클레오타이드에 편입되어 왔다 (Frieden 등, *Nucleic Acids Research*, 2003, 21, 6365-6372). 본 명세서에서, 이환형 뉴클레오사이드의 일반적인 설명은 두 이성질체 배치형태를 포함한다. 특이적 이환형 뉴클레오사이드 (예를 들면, LNA 또는 cEt)의 위치가 본 명세서에 예시된 구현예에서 확인되는 경우, 이들은, 달리 명시되지 않는 한, β-D 배치형태이다.

[0266] 특정 구현예에서, 변형된 당 모이어티는 하나 이상의 비-브릿징 당 치환체 및 하나 이상의 브릿징 당 치환체 (예를 들면, 5'-치환된 및 4'-2' 브릿징된 당)을 포함한다.

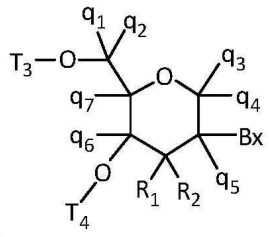
[0267] 특정 구현예에서, 변형된 당 모이어티는 당 대리물이다. 특정 상기 구현예에서, 당 모이어티의 산소 원자는, 예를 들면, 황, 탄소 또는 질소 원자로 대체된다. 특정 상기 구현예에서, 그와 같은 변형된 당 모이어티는 또한 본 명세서에 기재된 바와 같은 브릿징 및/또는 비-브릿징 치환체를 포함한다. 예를 들어, 특정 당 대리물은 2'-위치 (참고, 예를 들면, Bhat 등, U.S. 7,875,733 및 Bhat 등, U.S. 7,939,677) 및/또는 5' 위치에서 치환 및 4'-황 원자를 포함한다.

[0268] 특정 구현예에서, 당 대리물은 5개 원자 이외를 가지고 있는 고리를 포함한다. 예를 들어, 특정 구현예에서, 당 대리물은 6-원 테트라하이드로피란 ("THP")를 포함한다. 그와 같은 테트라하이드로피란은 추가로 변형 또는 치환될 수 있다. 그와 같은 변형된 테트라하이드로피란을 포함하는 뉴클레오사이드는 비제한적으로 하기를 포함한다: 헥시톨 핵산 ("HNA"), 아니톨 핵산 ("ANA"), 만니톨 핵산 ("MNA") (참고, 예를 들면, Leumann, CJ.Bioorg.& Med. Chem.2002, 10, 841-854), 플루오로 HNA:

[0269] 

[0270] F-HNA

[0271] ("F-HNA", 참고 예를 들어 Swayze 등, U.S. 8,088,904; Swayze 등, U.S. 8,440,803; Swayze 등, U.S. 8,796,437; 및 Swayze 등, U.S. 9,005,906; F-HNA는 또한 F-THP 또는 3'-플루오로 테트라하이드로피란으로서 지칭될 수 있다), 및 하기 식을 가지고 있는 추가의 변형된 THP 화합물을 포함하는 뉴클레오사이드:

[0272] 

[0273] 여기서, 독립적으로, 상기 변형된 THP 뉴클레오사이드의 각각에 대하여:

[0274] Bx는 핵염기 모이어티이고;

[0275] T_3 및 T_4 각각은, 독립적으로, 올리고뉴클레오타이드의 나머지에 변형된 THP 뉴클레오사이드를 결합시키는 인터뉴클레오사이드 결합기이거나 T_3 및 T_4 중 하나는 올리고뉴클레오타이드의 나머지에 변형된 THP 뉴클레오사이드

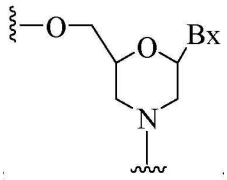
를 결합시키는 인터뉴클레오사이드 결합기이고 T_3 및 T_4 중 다른 하나는 H, 하이드록실 보호기, 연결된 컨쥬게이트 그룹, 또는 5' 또는 3'-말단기이고;

[0276] q_1, q_2, q_3, q_4, q_5, q_6 및 q_7 각각은, 독립적으로, H, C_1-C_6 알킬, 치환된 C_1-C_6 알킬, C_2-C_6 알케닐, 치환된 C_2-C_6 알케닐, C_2-C_6 알키닐, 또는 치환된 C_2-C_6 알키닐이고;

[0277] 각각의 R_1 및 R_2는 하기중으로부터 독립적으로 선택된다: 수소, 할로겐, 치환된 또는 미치환된 알콕시, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$, 및 CN, 여기서 X는 O, S 또는 NJ_1이고, 각 J_1, J_2, 및 J_3은, 독립적으로, H 또는 C_1-C_6 알킬임.

[0278] 특정 구현예에서, q_1, q_2, q_3, q_4, q_5, q_6 및 q_7 각각이 H인 변형된 THP 뉴클레오사이드는 제공된다. 특정 구현예에서, q_1, q_2, q_3, q_4, q_5, q_6 및 q_7 중 적어도 하나는 H 이외이다. 특정 구현예에서, q_1, q_2, q_3, q_4, q_5, q_6 및 q_7 중 적어도 하나는 메틸이다. 특정 구현예에서, R_1 및 R_2 중 하나가 F인 변형된 THP 뉴클레오사이드는 제공된다. 특정 구현예에서, R_1은 F이고 R_2는 H이고, 특정 구현예에서, R_1은 메톡시이고 R_2는 H이고, 특정 구현예에서, R_1은 메톡시에톡시이고 R_2는 H이다.

[0279] 특정 구현예에서, 당 대리물은 5개 초과 원자 및 1개 초과 헤테로원자를 가지고 있는 고리를 포함한다. 예를 들어, 올리고뉴클레오타이드에서 모폴리노 당 모이어티를 포함하는 뉴클레오사이드 및 이의 용도는 보고되어 왔다 (참고, 예를 들면, Braasch 등, Biochemistry, 2002, 41, 4503-4510 및 Summerton 등, U.S. 5,698,685; Summerton 등, U.S. 5,166,315; Summerton 등, U.S. 5,185,444; 및 Summerton 등, U.S. 5,034,506). 여기에서 사용된 바와 같이, 용어 "모폴리노"는 하기 구조를 가지고 있는 당 대리물을 의미한다:

[0280] 

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[0281] 특정 구현예에서, 모폴리노는, 예를 들어 상기 모폴리노 구조로부터 다양한 치환기 첨가 또는 변경에 의해 변형될 수 있다. 그와 같은 당 대리물은 본 명세서에서 "변형된 모폴리노"로서 지칭된다.

[0282] 특정 구현예에서, 당 대리물은 비환형 모이에이티를 포함한다. 그와 같은 비환형 당 대리물을 포함하는 뉴클레오사이드 및 올리고뉴클레오타이드의 예는 하기를 비제한적으로 포함한다: 펩타이드 핵산 ("PNA"), 비환형 부틸 핵산 (참고, 예를 들면, Kumar 등, *Org. Biomol. Chem.*, 2013, 11, 5853-5865), 및 Manoharan 등, WO2011/133876에서 기재된 뉴클레오사이드 및 올리고뉴클레오타이드.

[0283] 많은 다른 이환형 및 삼환형 당 및 당 대리물 고리계는 변형된 뉴클레오사이드에서 사용될 수 있는 당해 기술에 공지되어 있다).

[0284] **2. 특정 변형된 핵염기**

[0285] 특정 구현예에서, 변형된 올리고뉴클레오타이드는 미변형된 핵염기를 포함하는 하나 이상의 뉴클레오사이드를 포함한다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 변형된 핵염기를 포함하는 하나 이상의 뉴클레오사이드를 포함한다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는, 무염기성 뉴클레오사이드로서 지칭된, 핵염기를 포함하지 않는 하나 이상의 뉴클레오사이드를 포함한다.

[0286] 특정 구현예에서, 변형된 핵염기는 하기로부터 선택된다: 5-치환된 피리미딘, 6-아자피리미딘, 알킬 또는 알키닐 치환된 피리미딘, 알킬 치환된 퓨린, 및 N-2, N-6 및 O-6 치환된 퓨린. 특정 구현예에서, 변형된 핵염기는 하기로부터 선택된다: 2-아미노프로필아데닌, 5-하이드록시메틸 시토신, 잔틴, 하이포잔틴, 2-아미노아데닌, 6-N-메틸구아닌, 6-N-메틸아데닌, 2-프로필아데닌 , 2-티오우라실, 2-티오티민 및 2-티오시토신, 5-프로피닐 (-C≡C-CH_3) 우라실, 5-프로피닐시토신, 6-아조우라실, 6-아조시토신, 6-아조티민, 5-리보실우라실 (슈도우라실), 4-티오우라실, 8-할로, 8-아미노, 8-티올, 8-티오알킬, 8-하이드록실, 8-아자 및 다른 8-치환된 퓨린, 5-할로, 특히 5-브로모, 5-트리플루오로메틸, 5-할로우라실, 및 5-할로시토신, 7-메틸구아닌, 7-메틸아데닌, 2-F-아데닌, 2-아미노아데닌, 7-데아자구아닌, 7-데아자아데닌, 3-데아자구아닌, 3-데아자아데닌, 6-N-벤조일아

데닌, 2-N-이소부티릴구아닌, 4-N-벤조일시토신, 4-N-벤조일우라실, 5-메틸 4-N-벤조일시토신, 5-메틸 4-N-벤조일우라실, 보편적인 염기, 소수성 염기, 부정확한 염기, 크기-팽창된 염기, 및 플루오르화된 염기. 추가 변형된 핵염기는 삼환형 피리미딘, 예컨대 1,3-디아자펜옥사진-2-온, 1,3-디아자페노티아진-2-온 및 9-(2-아미노에톡시)-1,3-디아자펜옥사진-2-온 (G-클램프)를 포함한다. 변형된 핵염기는 또한 퓨린 또는 피리미딘이 다른 헤테로사이클, 예를 들어 7-데아자-아데닌, 7-데아자구아노신, 2-아미노피리딘 및 2-피리돈으로 대체되는 것들을 포함할 수 있다. 추가 핵염기는 Merigan 등, U.S. 3,687,808에서 개시된 것, *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J.I., Ed., John Wiley & Sons, 1990, 858-859; Englisch 등, *Angewandte Chemie*, International Edition, 1991, 30, 613; Sanghvi, Y.S., Chapter 15, *Antisense Research and Applications*, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993, 273-288에서 개시된 것; 및 Chapters 6 and 15, *Antisense Drug Technology*, Crooke S.T., Ed., CRC Press, 2008, 163-166 및 442-443에서 개시된 것을 포함한다.

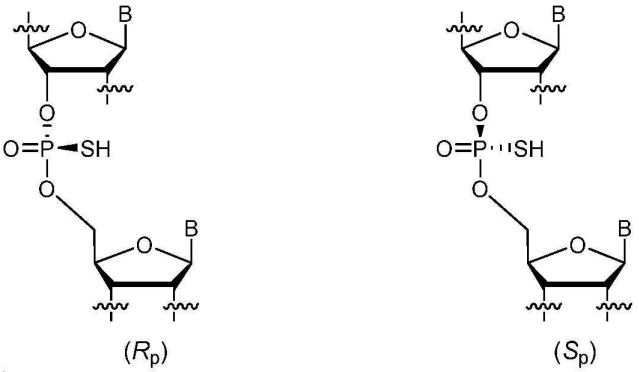
[0287] 특정 상기 언급된 변형된 핵염기 뿐만 아니라 다른 변형된 핵염기의 제조를 교시하는 공보는 제한 없이, 하기를 포함한다: Manohara 등, US2003/0158403; Manoharan 등, US2003/0175906; Dinh 등, U.S. 4,845,205; Spielvogel 등, U.S. 5,130,302; Rogers 등, U.S. 5,134,066; Bischofberger 등, U.S. 5,175,273; Urdea 등, U.S. 5,367,066; Benner 등, U.S. 5,432,272; Matteucci 등, U.S. 5,434,257; Gmeiner 등, U.S. 5,457,187; Cook 등, U.S. 5,459,255; Froehler 등, U.S. 5,484,908; Matteucci 등, U.S. 5,502,177; Hawkins 등, U.S. 5,525,711; Haralambidis 등, U.S. 5,552,540; Cook 등, U.S. 5,587,469; Froehler 등, U.S. 5,594,121; Switzer 등, U.S. 5,596,091; Cook 등, U.S. 5,614,617; Froehler 등, U.S. 5,645,985; Cook 등, U.S. 5,681,941; Cook 등, U.S. 5,811,534; Cook 등, U.S. 5,750,692; Cook 등, U.S. 5,948,903; Cook 등, U.S. 5,587,470; Cook 등, U.S. 5,457,191; Matteucci 등, U.S. 5,763,588; Froehler 등, U.S. 5,830,653; Cook 등, U.S. 5,808,027; Cook 등, 6,166,199; 및 Matteucci 등, U.S. 6,005,096.

[0288] **3. 특정 변형된 인터뉴클레오사이드 연결기**

[0289] 특정 구현예에서, 변형된 올리고뉴클레오타이드의 뉴클레오사이드는 임의의 인터뉴클레오사이드 연결기를 사용하여 함께 연결될 수 있다. 인터뉴클레오사이드 결합기의 2개의 주요 부류는 인 원자의 존재 또는 부재에 의해 정의된다. 대표적인 인-함유 인터뉴클레오사이드 연결기는 비제한적으로 포스페이트를 포함하고, 이는 포스포디에스테르 결합 ("P=O") (미변형된 또는 자연 발생 연결기로도 칭함), 포스포트리에스테르, 메틸포스포네이트, 포스포르아미데이트, 및 포스포로티오에이트 ("P=S"), 및 포스포로디티오에이트 ("HS-P=S")를 함유한다. 대표적인 비-인 함유 인터뉴클레오사이드 결합기는 비제한적으로 메틸렌메틸이미노 ($-CH_2-N(CH_3)-O-CH_2-$), 티오디에스테르, 티오노카바메이트 (-O-C(=O)(NH)-S-); 실록산 ($-O-SiH_2-O-$); 및 N,N'-디메틸하이드라진 ($-CH_2-N(CH_3)-N(CH_3)-$)을 포함한다. 자연 발생 포스페이트 연결기에 비교된, 변형된 인터뉴클레오사이드 연결기는 올리고뉴클레오타이드의 뉴클레아제 내성을 변경, 전형적으로 증가시키는데 사용될 수 있다. 특정 구현예에서, 키랄 원자를 가지고 있는 인터뉴클레오사이드 연결기는 라세미 혼합물로서, 또는 별도의 거울상이성질체로서 제조될 수 있다. 인함유 및 비-인함유 인터뉴클레오사이드 연결기의 제조 방법은 당해 분야의 숙련가에게 잘 알려진다.

[0290] 키랄 중심을 가지고 있는 대표적인 인터뉴클레오사이드 연결기는 비제한적으로 알킬포스포네이트 및 포스포로티오에이트를 포함한다. 키랄 중심을 가지고 있는 인터뉴클레오사이드 연결기를 포함하는 변형된 올리고뉴클레오타이드는 스테레오랜덤 인터뉴클레오사이드 연결기를 포함하는 변형된 올리고뉴클레오타이드의 집단으로서, 또는 특정 입체화학적 배치형태로 포스포로티오에이트 연결기를 포함하는 변형된 올리고뉴클레오타이드의 집단으로서 제조될 수 있다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 집단은 모든 포스포로티오에이트 인터뉴클레오사이드 연결기가 스테레오랜덤인 포스포로티오에이트 인터뉴클레오사이드 연결기를 포함한다. 그와 같은 변형된 올리고뉴클레오타이드는 각 포스포로티오에이트 연결기의 입체화학적 배치형태의 랜덤 선택을 초래하는 합성 방법을 사용하여 생성될 수 있다. 그럼에도 불구하고, 당해 분야의 숙련가에 의해 잘 이해되는 바와 같이, 각 개별 올리고뉴클레오타이드 분자의 각 개별 포스포로티오에이트는 정의된 배치형태를 갖는다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 집단은 특정, 독립적으로 선택된 입체화학적 배치형태에서 하나 이상의 특정 포스포로티오에이트 인터뉴클레오사이드 연결기를 포함하는 변형된 올리고뉴클레오타이드가 풍부하다. 특정 구현예에서, 특정 포스포로티오에이트 연결기의 특정 배치형태는 집단에서 분자의 적어도 65%에서 존재한다. 특정 구현예에서, 특정 포스포로티오에이트 연결기의 특정 배치형태는 집단에서 분자의 적어도 70%에서 존재한다. 특정 구현예에서, 특정 포스포로티오에이트 연결기의 특정 배치형태는 집단에서 분자의 적어도 80%에서 존재한다. 특정 구현예에서, 특정 포스포로티오에이트 연결기의 특정 배치형태는 집단에서 분자의 적어도 90%에서

존재한다. 특정 구현예에서, 특정 포스포로티오에이트 연결기의 특정 배치형태는 집단에서 분자의 적어도 99%에서 존재한다. 변형된 올리고뉴클레오타이드의 그와 같은 키랄 풍부 집단은 당업계에서 알려진 합성 방법, 예를 들면, Oka 등, *JACS* 125, 8307 (2003), Wan 등. *Nuc. Acid. Res.* 42, 13456 (2014), 및 WO 2017/015555에서 기재된 방법을 사용하여 생성될 수 있다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 집단은 (Sp) 배치형태에서 적어도 하나의 지시된 포스포로티오에이트를 가지고 있는 변형된 올리고뉴클레오타이드가 풍부하다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 집단은 (Rp) 배치형태에서 적어도 하나의 포스포로티오에이트를 가지고 있는 변형된 올리고뉴클레오타이드가 풍부하다. 특정 구현예에서, (Rp) 및/또는 (Sp) 포스포로티오에이트를 포함하는 변형된 올리고뉴클레오타이드는, "B"가 핵염기를 나타내는, 하나 이상의 하기 식, 각각을 포함한다:

[0291] 

[0292] 달리 나타내지 않는 한, 본 명세서에 기재된 변형된 올리고뉴클레오타이드의 키랄 인터뉴클레오사이드 연결기는 스테레오랜덤일 수 있거나 특정 입체화학적 배치형태일 수 있다.

[0293] 중성 인터뉴클레오사이드 연결기는, 제한 없이, 포스포트리에스테르, 메틸포스포네이트, MMI (3'-CH_2-N(CH_3)-O-5'), 아미드-3 (3'-CH_2-C(=O)-N(H)-5'), 아미드-4 (3'-CH_2-N(H)-C(=O)-5'), 포름아세탈 (3'-O-CH_2-O-5'), 메톡시프로필, 및 티오포름아세탈 (3'-S-CH_2-O-5')를 포함한다. 추가 중성 인터뉴클레오사이드 연결기는 실록산 (디알킬실록산), 카복실레이트 에스테르, 카복사미드, 설파이드, 설포네이트 에스테르 및 아미드를 포함하는 비이온성 연결기를 포함한다 (참고 예를 들어: *Carbohydrate Modifications in Antisense Research*; Y. S. Sanghvi and P. D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). 추가 중성 인터뉴클레오사이드 연결기는 혼합된 N, O, S 및 CH_2 성분 부분을 포함하는 비이온성 연결기를 포함한다.

[0294] **B. 특정 모티프**

[0295] 특정 구현예에서, 변형된 올리고뉴클레오타이드는 변형된 당 모이어티를 포함하는 하나 이상의 변형된 뉴클레오사이드를 포함한다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 변형된 핵염기를 포함하는 하나 이상의 변형된 뉴클레오사이드를 포함한다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 하나 이상의 변형된 인터뉴클레오사이드 연결기를 포함한다. 상기 구현예에서, 변형된 올리고뉴클레오타이드의 변형된, 미변형된, 및 상이하게 변형된 당 모이어티, 핵염기, 및/또는 인터뉴클레오사이드 연결기는 패턴 또는 모티프를 정의한다. 특정 구현예에서, 당 모이어티, 핵염기, 및 인터뉴클레오사이드 연결기의 패턴 각각은 서로 독립적이다. 따라서, 변형된 올리고뉴클레오타이드는 그것의 당 모티프, 핵염기 모티프 및/또는 인터뉴클레오사이드 연결기 모티프에 의해 기재될 수 있다 (본 명세서에 사용된 바와 같이, 핵염기 모티프는 핵염기의 서열에 독립적인 핵염기에 대한 변형을 기재한다).

[0296] **1. 특정 당 모티프**

[0297] 특정 구현예에서, 올리고뉴클레오타이드는 정의된 패턴 또는 당 모티프에서 올리고뉴클레오타이드 또는 이의 영역을 따라 배열된 변형된 당 및/또는 미변형된 당 모이어티의 하나 이상의 유형을 포함한다. 특정 사례에서, 그와 같은 당 모티프는 비제한적으로 본 명세서에 논의된 임의의 당 변형을 포함한다.

[0298] 특정 구현예에서, 변형된 올리고뉴클레오타이드는, 2개의 외부 영역 즉 "윙" 그리고 중심 또는 내부 영역 즉 "갭"에 의해 정의되는, 갭머 모티프를 가지고 있는 영역을 포함하거나 상기로 이루어진다. 갭머 모티프의 3개의 영역 (5'-윙, 갭, 및 3'-윙)은 윙의 각각의 뉴클레오사이드의 당 모이어티의 적어도 일부가 갭의 뉴클레오사이드의 당 모이어티의 적어도 일부와 상이한 뉴클레오사이드의 연속적 서열을 형성한다. 구체적으로, 갭에 가장

가까운 각 윙의 뉴클레오사이드 (5'-윙의 3'-최말단 뉴클레오사이드 및 3'-윙의 5'-최말단 뉴클레오사이드)의 적어도 당 모이어티는 이웃한 갭 뉴클레오사이드의 당 모이어티와 상이하고, 따라서 윙들과 갭 사이 경계 (즉, 윙/갭 접합)을 정의한다. 특정 구현예에서, 갭 내에서 당 모이어티는 서로 동일하다. 특정 구현예에서, 갭은 갭의 하나 이상의 다른 뉴클레오사이드의 당 모이어티와 상이한 당 모이어티를 가지고 있는 하나 이상의 뉴클레오사이드를 포함한다. 특정 구현예에서, 2개 윙의 당 모티프는 서로 (대칭 갭머) 동일하다. 특정 구현예에서, 5'-윙의 당 모티프는 3'-윙 (비대칭 갭머)의 당 모티프와 상이하다.

[0299] 특정 구현예에서, 갭머의 윙은 1-5개의 뉴클레오사이드를 포함한다. 특정 구현예에서, 갭머의 각 윙의 각 뉴클레오사이드는 변형된 뉴클레오사이드이다. 특정 구현예에서, 갭머의 각 윙의 적어도 1개의 뉴클레오사이드는 변형된 뉴클레오사이드이다. 특정 구현예에서, 갭머의 각 윙의 적어도 2개의 뉴클레오사이드는 변형된 뉴클레오사이드이다. 특정 구현예에서, 갭머의 각 윙의 적어도 3개의 뉴클레오사이드는 변형된 뉴클레오사이드이다. 특정 구현예에서, 갭머의 각 윙의 적어도 4개의 뉴클레오사이드는 변형된 뉴클레오사이드이다.

[0300] 특정 구현예에서, 갭머의 갭은 7-12개의 뉴클레오사이드를 포함한다. 특정 구현예에서, 갭머의 갭의 각 뉴클레오사이드는 미변형된 2'-데옥시 뉴클레오사이드이다. 특정 구현예에서, 갭머의 갭의 적어도 1개의 뉴클레오사이드는 변형된 뉴클레오사이드이다.

[0301] 특정 구현예에서, 갭머는 데옥시 갭머이다. 특정 구현예에서, 각 윙/갭 접합의 갭 측에서 뉴클레오사이드는 미변형된 2'-데옥시 뉴클레오사이드이고 각 윙/갭 접합의 윙 측에서 뉴클레오사이드는 변형된 뉴클레오사이드이다. 특정 구현예에서, 갭의 각 뉴클레오사이드는 미변형된 2'-데옥시 뉴클레오사이드이다. 특정 구현예에서, 갭머의 각 윙의 각 뉴클레오사이드는 변형된 뉴클레오사이드이다.

[0302] 특정 구현예에서, 변형된 올리고뉴클레오타이드는 완전하게 변형된 당 모티프를 가지고 있는 영역을 포함하거나 상기로 이루어진다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 완전하게 변형된 영역의 각 뉴클레오사이드는 변형된 당 모이어티를 포함한다. 특정 구현예에서, 전체 변형된 올리고뉴클레오타이드의 각 뉴클레오사이드는 변형된 당 모이어티를 포함한다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 완전하게 변형된 당 모티프를 가지고 있는 영역을 포함하거나 상기로 이루어지고, 여기서 완전하게 변형된 영역 내에서 각 뉴클레오사이드는, 본 명세서에서 균일하게 변형된 당 모티프로서 지칭된, 동일한 변형된 당 모이어티를 포함한다. 특정 구현예에서, 완전하게 변형된 올리고뉴클레오타이드는 균일하게 변형된 올리고뉴클레오타이드이다. 특정 구현예에서, 균일하게 변형된의 각 뉴클레오사이드는 동일한 2'-변형을 포함한다.

[0303] 본 명세서에, 갭머의 3개의 영역의 길이 (뉴클레오사이드의 수)는 표기법 [5'-윙에서 뉴클레오사이드의 #] - [갭에서 뉴클레오사이드의 #] - [3'-윙에서 뉴클레오사이드의 #]를 사용하여 제공될 수 있다. 따라서, 5-10-5 갭머는 각 윙에서 5개의 연결된 뉴클레오사이드 및 갭에서 10개의 연결된 뉴클레오사이드로 이루어진다. 그와 같은 명명법이 특정 변형에 뒤따르는 경우, 그 변형은 각 윙의 각 당 모이어티에서 변형이고 갭 뉴클레오사이드는 미변형된 데옥시뉴클레오사이드 당을 포함한다. 따라서, 5-10-5 MOE 갭머는 5'-윙에서 5개의 연결된 MOE 변형된 뉴클레오사이드, 갭에서 10개의 연결된 데옥시뉴클레오사이드, 그리고 3'-윙에서 5개의 연결된 MOE 뉴클레오사이드로 이루어진다.

[0304] 특정 구현예에서, 변형된 올리고뉴클레오타이드는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 3-10-3 BNA 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 3-10-3 cEt 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 3-10-3 LNA 갭머이다.

[0305] **2. 특정 핵염기 모티프**

[0306] 특정 구현예에서, 올리고뉴클레오타이드는 정의된 패턴 또는 모티프에서 올리고뉴클레오타이드 또는 이의 영역을 따라 배열된 변형된 및/또는 미변형된 핵염기를 포함한다. 특정 구현예에서, 각 핵염기는 변형된다. 특정 구현예에서, 핵염기의 어느 것도 변형되지 않는다. 특정 구현예에서, 각 퓨린 또는 각 피리미딘은 변형된다. 특정 구현예에서, 각 아데닌은 변형된다. 특정 구현예에서, 각 구아닌은 변형된다. 특정 구현예에서, 각 티민은 변형된다. 특정 구현예에서, 각 우라실은 변형된다. 특정 구현예에서, 각 시토신은 변형된다. 특정 구현예에서, 변형된 올리고뉴클레오타이드에서 일부 또는 모든 시토신 핵염기는 5-메틸 시토신이다. 특정 구현예에서, 시토신 핵염기의 모두는 5-메틸 시토신이고 변형된 올리고뉴클레오타이드의 다른 핵염기의 모두는 미변형된 핵염기이다.

[0307] 특정 구현예에서, 변형된 올리고뉴클레오타이드는 변형된 핵염기의 블록을 포함한다. 특정 상기 구현예에서, 블록은 올리고뉴클레오타이드의 3'-말단에 있다. 특정 구현예에서 블록은 올리고뉴클레오타이드의 3'-말단의 3개

뉴클레오사이드 내에 있다. 특정 구현예에서, 블록은 올리고뉴클레오타이드의 5'-말단에 있다. 특정 구현예에서 블록은 올리고뉴클레오타이드의 5'-말단의 3개 뉴클레오사이드 내에 있다.

[0308] 특정 구현예에서, 갭머 모티프를 가지고 있는 올리고뉴클레오타이드는 변형된 핵염기를 포함하는 뉴클레오사이드를 포함한다. 특정 상기 구현예에서, 변형된 핵염기를 포함하는 1개의 뉴클레오사이드는 갭머 모티프를 가지고 있는 올리고뉴클레오타이드의 중심 갭에 있다. 특정 상기 구현예에서, 상기 뉴클레오사이드의 당 모이어티는 2'-데옥시리보실 모이어티이다. 특정 구현예에서, 변형된 핵염기는 하기로부터 선택된다: 2-티오피리미딘 및 5-프로핀피리미딘.

[0309] 3. 특정 인터뉴클레오사이드 연결기 모티프

[0310] 특정 구현예에서, 올리고뉴클레오타이드는 정의된 패턴 또는 모티프에서 올리고뉴클레오타이드 또는 이의 영역을 따라 배열된 변형된 및/또는 미변형된 인터뉴클레오사이드 연결기를 포함한다. 특정 구현예에서, 각 인터뉴클레오사이드 결합기는 포스포디에스테르 인터뉴클레오사이드 연결기 (P=O)이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 각 인터뉴클레오사이드 결합기는 포스포로티오에이트 인터뉴클레오사이드 연결기 (P=S)이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 각 인터뉴클레오사이드 연결기는 독립적으로 포스포로티오에이트 인터뉴클레오사이드 연결기 및 포스포디에스테르 인터뉴클레오사이드 연결기로부터 선택된다. 특정 구현예에서, 각 포스포로티오에이트 인터뉴클레오사이드 연결기는 독립적으로 스테레오랜덤 포스포로티오에이트, (Sp) 포스포로티오에이트, 및 (Rp) 포스포로티오에이트로부터 선택된다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 당 모티프는 갭머이고 갭 내에서 인터뉴클레오사이드 연결기 모두는 변형된다. 특정 상기 구현예에서, 윙에서 일부 또는 모든 인터뉴클레오사이드 연결기는 미변형된 포스포디에스테르 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 말단 인터뉴클레오사이드 연결기는 변형된다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 당 모티프는 갭머이고, 인터뉴클레오사이드 연결기 모티프는 적어도 하나의 윙에서 적어도 하나의 포스포디에스테르 인터뉴클레오사이드 연결기를 포함하고, 여기서 상기 적어도 하나의 포스포디에스테르 연결기는 말단 인터뉴클레오사이드 연결기가 아니고, 나머지 인터뉴클레오사이드 연결기는 포스포로티오에이트 인터뉴클레오사이드 연결기이다. 특정 상기 구현예에서, 모든 포스포로티오에이트 연결기는 스테레오랜덤이다. 특정 구현예에서, 윙에서 모든 포스포로티오에이트 연결기는 (Sp) 포스포로티오에이트이고, 갭은 적어도 하나의 Sp, Sp, Rp 모티프를 포함한다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 집단은 그와 같은 인터뉴클레오사이드 연결기 모티프를 포함하는 변형된 올리고뉴클레오타이드가 풍부하다.

[0311] C. 특정 길이

[0312] 활성 제거 없이 올리고뉴클레오타이드의 길이를 증가 또는 감소하는 것은 가능하다. 예를 들어, Woolf 등 (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992)에서, 13-25개의 핵염기 길이의 일련의 올리고뉴클레오타이드는 난모세포 주입 모델에서 표적 RNA의 절단을 유도하기 위한 그들의 능력에 대하여 시험되었다. 올리고뉴클레오타이드의 말단 근처에 8 또는 11개의 미스매치 염기가 있는 25개의 핵염기 길이의 올리고뉴클레오타이드는, 미스매치를 함유하지 않았던 올리고뉴클레오타이드보다 더 적은 정도에도 불구하고, 표적 RNA의 특이적 절단을 유도할 수 있었다. 유사하게, 표적 특이적 절단은, 1 또는 3개의 미스매치가 있는 것을 포함하여, 13개의 핵염기 올리고뉴클레오타이드를 사용하여 달성되었다.

[0313] 특정 구현예에서, (변형된 올리고뉴클레오타이드를 포함하는) 올리고뉴클레오타이드는 임의의 다양한 범위의 길이를 가질 수 있다. 특정 구현예에서, 올리고뉴클레오타이드는 X 내지 Y개의 연결된 뉴클레오사이드로 이루어지고, 여기에서 X는 범위에서 뉴클레오사이드의 가장 적은 수를 나타내고 Y는 범위에서 최대 수 뉴클레오사이드를 나타낸다. 특정 상기 구현예에서, X 및 Y는 각각 독립적으로 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 및 50으로부터 선택된다; 단 X≤Y. 예를 들어, 특정 구현예에서, 올리고뉴클레오타이드는 12 내지 13, 12 내지 14, 12 내지 15, 12 내지 16, 12 내지 17, 12 내지 18, 12 내지 19, 12 내지 20, 12 내지 21, 12 내지 22, 12 내지 23, 12 내지 24, 12 내지 25, 12 내지 26, 12 내지 27, 12 내지 28, 12 내지 29, 12 내지 30, 13 내지 14, 13 내지 15, 13 내지 16, 13 내지 17, 13 내지 18, 13 내지 19, 13 내지 20, 13 내지 21, 13 내지 22, 13 내지 23, 13 내지 24, 13 내지 25, 13 내지 26, 13 내지 27, 13 내지 28, 13 내지 29, 13 내지 30, 14 내지 15, 14 내지 16, 14 내지 17, 14 내지 18, 14 내지 19, 14 내지 20, 14 내지 21, 14 내지 22, 14 내지 23, 14 내지 24, 14 내지 25, 14 내지 26, 14 내지 27, 14 내지 28, 14 내지 29, 14 내지 30, 15 내지 16, 15 내지 17, 15 내지 18, 15 내지 19, 15 내지 20, 15 내지 21, 15 내지 22, 15 내지 23, 15 내지 24, 15 내지 25, 15 내지 26, 15 내지 27, 15 내지 28, 15 내지 29, 15 내지 30, 16 내지 17, 16 내지 18, 16

내지 19, 16 내지 20, 16 내지 21, 16 내지 22, 16 내지 23, 16 내지 24, 16 내지 25, 16 내지 26, 16 내지 27, 16 내지 28, 16 내지 29, 16 내지 30, 17 내지 18, 17 내지 19, 17 내지 20, 17 내지 21, 17 내지 22, 17 내지 23, 17 내지 24, 17 내지 25, 17 내지 26, 17 내지 27, 17 내지 28, 17 내지 29, 17 내지 30, 18 내지 19, 18 내지 20, 18 내지 21, 18 내지 22, 18 내지 23, 18 내지 24, 18 내지 25, 18 내지 26, 18 내지 27, 18 내지 28, 18 내지 29, 18 내지 30, 19 내지 20, 19 내지 21, 19 내지 22, 19 내지 23, 19 내지 24, 19 내지 25, 19 내지 26, 19 내지 29, 19 내지 28, 19 내지 29, 19 내지 30, 20 내지 21, 20 내지 22, 20 내지 23, 20 내지 24, 20 내지 25, 20 내지 26, 20 내지 27, 20 내지 28, 20 내지 29, 20 내지 30, 21 내지 22, 21 내지 23, 21 내지 24, 21 내지 25, 21 내지 26, 21 내지 27, 21 내지 28, 21 내지 29, 21 내지 30, 22 내지 23, 22 내지 24, 22 내지 25, 22 내지 26, 22 내지 27, 22 내지 28, 22 내지 29, 22 내지 30, 23 내지 24, 23 내지 25, 23 내지 26, 23 내지 27, 23 내지 28, 23 내지 29, 23 내지 30, 24 내지 25, 24 내지 26, 24 내지 27, 24 내지 28, 24 내지 29, 24 내지 30, 25 내지 26, 25 내지 27, 25 내지 28, 25 내지 29, 25 내지 30, 26 내지 27, 26 내지 28, 26 내지 29, 26 내지 30, 27 내지 28, 27 내지 29, 27 내지 30, 28 내지 29, 28 내지 30, 또는 29 내지 30개의 연결된 뉴클레오사이드로 이루어진다.

[0314] **D. 특정 변형된 올리고뉴클레오타이드**

[0315] 특정 구현예에서, 상기 변형 (당, 핵염기, 인터뉴클레오사이드 연결기)는 변형된 올리고뉴클레오타이드 속에 편입된다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 그들의 변형 모티프 및 전체적인 길이를 특징으로 한다. 특정 구현예에서, 그와 같은 파라미터 각각은 서로 독립적이다. 따라서, 달리 나타내지 않는 한, 갭머 당 모티프를 가지고 있는 올리고뉴클레오타이드의 각 인터뉴클레오사이드 연결기는 변형될 수 있거나 미변형될 수 있고 당 변형의 갭머 변형 패턴을 따를 수 있거나 따르지 않을 수 있다. 예를 들어, 당 갭머의 윙 영역 내에서 인터뉴클레오사이드 연결기는 서로 동일 또는 상이할 수 있고 당 모티프의 갭 영역의 인터뉴클레오사이드 연결기와 동일 또는 상이할 수 있다. 마찬가지로, 그와 같은 당 갭머 올리고뉴클레오타이드는 당 변형의 갭머 패턴과 독립적인 하나 이상의 변형된 핵염기를 포함할 수 있다. 달리 나타내지 않는 한, 모든 변형은 핵염기 서열과 독립적이다.

[0316] **E. 변형된 올리고뉴클레오타이드의 특정 집단**

[0317] 집단의 모든 변형된 올리고뉴클레오타이드가 동일한 분자식을 갖는 변형된 올리고뉴클레오타이드의 집단은 스테레오랜덤 집단 또는 키랄 풍부 집단일 수 있다. 모든 변형된 올리고뉴클레오타이드의 모든 키랄 중심은 스테레오랜덤 집단에서 스테레오랜덤이다. 키랄 풍부 집단에서, 적어도 하나의 특정 키랄 중심은 집단의 변형된 올리고뉴클레오타이드에서 스테레오랜덤이 아니다. 특정 구현예에서, 키랄 풍부 집단의 변형된 올리고뉴클레오타이드는 β-D 리보실 당 모이어티가 풍부하고, 모든 포스포로티오에이트 인터뉴클레오사이드 연결기는 스테레오랜덤이다. 특정 구현예에서, 키랄 풍부 집단의 변형된 올리고뉴클레오타이드는 특정 입체화학적 배치형태에서 β-D 리보실 당 모이어티 및 적어도 하나의, 특정 포스포로티오에이트 인터뉴클레오사이드 연결기 둘 모두가 풍부하다.

[0318] **F. 핵염기 서열**

[0319] 특정 구현예에서, 올리고뉴클레오타이드 (미변형된 또는 변형된 올리고뉴클레오타이드)는 그들의 핵염기 서열에 의해 추가로 기재된다. 특정 구현예에서 올리고뉴클레오타이드는 제2 올리고뉴클레오타이드 또는 확인된 참고 핵산, 예컨대 표적 핵산에 상보성인 핵염기 서열을 가지고 있다. 특정 상기 구현예에서, 올리고뉴클레오타이드의 영역은 제2 올리고뉴클레오타이드 또는 확인된 참고 핵산, 예컨대 표적 핵산에 상보성인 핵염기 서열을 갖는다. 특정 구현예에서, 올리고뉴클레오타이드의 영역 또는 전체 길이의 핵염기 서열은 제2 올리고뉴클레오타이드 또는 핵산, 예컨대 표적 핵산에 적어도 50%, 적어도 60%, 적어도 70%, 적어도 80%, 적어도 85%, 적어도 90%, 적어도 95%, 또는 100% 상보성이다.

[0320] **II. 특정 올리고머성 화합물**

[0321] 특정 구현예에서, (변형된 또는 미변형된) 올리고뉴클레오타이드 및 선택적으로 하나 이상의 컨쥬게이트 그룹 및/또는 말단기로 이루어지는, 올리고머성 화합물은 본 명세서에 제공된다. 컨쥬게이트 그룹은 컨쥬게이트 모이어티를 올리고뉴클레오타이드에 결합시키는 하나 이상의 컨쥬게이트 모이어티 및 컨쥬게이트 링커로 이루어진다. 컨쥬게이트 그룹은 올리고뉴클레오타이드의 어느 한쪽 또는 양쪽 말단에 및/또는 임의의 내부 위치에 부착될 수 있다. 특정 구현예에서, 컨쥬게이트 그룹은 변형된 올리고뉴클레오타이드의 뉴클레오사이드의 2'-위치에 부착된다. 특정 구현예에서, 올리고뉴클레오타이드의 어느 한쪽 또는 양쪽 말단에 부착되는 컨쥬게이트

그룹은 말단기이다. 특정 상기 구현예에서, 컨쥬게이트 그룹 또는 말단기는 올리고뉴클레오타이드의 3' 및/또는 5'-말단에 부착된다. 특정 상기 구현예에서, 컨쥬게이트 그룹 (또는 말단기)는 올리고뉴클레오타이드의 3'-말단에 부착된다. 특정 구현예에서, 컨쥬게이트 그룹은 올리고뉴클레오타이드의 3'-말단 근처에 부착된다. 특정 구현예에서, 컨쥬게이트 그룹 (또는 말단기)는 올리고뉴클레오타이드의 5'-말단에 부착된다. 특정 구현예에서, 컨쥬게이트 그룹은 올리고뉴클레오타이드의 5'-말단 근처에 부착된다.

[0322] 말단기의 예는 비제한적으로 컨쥬게이트 그룹, 캡핑 그룹, 포스페이트 모이어티, 보호기, 변형된 또는 미변형된 뉴클레오사이드, 및 독립적으로 변형 또는 미변형되는 2개 이상의 뉴클레오사이드를 포함한다.

[0323] **A. 특정 컨쥬게이트 그룹**

[0324] 특정 구현예에서, 올리고뉴클레오타이드는 하나 이상의 컨쥬게이트 그룹에 공유적으로 부착된다. 특정 구현예에서, 컨쥬게이트 그룹은, 비제한적으로 약력학, 약동학, 안정성, 결합, 흡수, 조직 분포, 세포 분포, 세포 흡수, 충전 및 청소능을 포함하는, 부착된 올리고뉴클레오타이드의 하나 이상의 특성을 변형시킨다. 특정 구현예에서, 컨쥬게이트 그룹은 올리고뉴클레오타이드의 검출을 가능하게 하는 부착된 올리고뉴클레오타이드, 예를 들면, 형광단 또는 리포터 그룹에 신규한 특성을 부여한다. 특정 컨쥬게이트 그룹 및 컨쥬게이트 모이어티, 예를 들어 하기는 이전에 기재되어 왔다: 콜레스테롤 모이어티 (Letsinger 등, Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), 콜산 (Manoharan 등, *Bioorg. Med. Chem.Lett.*, 1994, *4*, 1053-1060), 티오에테르, 예를 들면, 헥실-S-트리틸티올 (Manoharan 등, *Ann. N.Y. Acad. Sci.*, 1992, 660, 306-309; Manoharan 등, *Bioorg. Med. Chem.Lett.*, 1993, 3, 2765-2770), 티오콜레스테롤 (Oberhauser 등, *Nucl. Acids Res.*, 1992, 20, 533-538), 지방족 사슬, 예를 들면, 도-데칸-디올 또는 운데실 잔기 (Saison-Behmoaras 등, *EMBO J.*, 1991, 10, 1111-1118; Kabanov 등, *FEBS Lett.*, 1990, 259, 327-330; Svinarchuk 등, *Biochimie*, 1993, 75, 49-54), 인지질, 예를 들면, 디-헥사데실-rac-글리세롤 또는 트리에틸-암모늄 1,2-디-O-헥사데실-rac-글리세로-3-H-포스포네이트 (Manoharan 등, *Tetrahedron Lett.*, 1995, 36, 3651-3654; Shea 등, *Nucl. Acids Res.*, 1990, 18, 3777-3783), 폴리아민 또는 폴리에틸렌 글리콜 사슬 (Manoharan 등, *Nucleosides & Nucleotides*, 1995, 14, 969-973), 또는 아다만탄 아세트산, 팔미틸 모이어티 (Mishra 등, *Biochim. Biophys. Acta*, 1995, 1264, 229-237), 옥타데실아민 또는 헥실아미노-카보닐-옥시콜레스테롤 모이어티 (Crooke 등, *J. Pharmacol.Exp. Ther.*, 1996, *i*, 923-937), 토코페롤 그룹 (Nishina 등, *Molecular Therapy Nucleic Acids*, 2015, 4, e220; 및 Nishina 등, *Molecular Therapy*, 2008, 16, 734-740), 또는 GalNAc 클러스터 (예를 들면, WO2014/179620).

[0325] **1. 컨쥬게이트 모이어티**

[0326] 컨쥬게이트 모이어티는, 제한 없이, 삽입제, 리포터 분자, 폴리아민, 폴리아미드, 펩타이드, 탄수화물, 비타민 모이어티, 폴리에틸렌 글리콜, 티오에테르, 폴리에테르, 콜레스테롤, 티오콜레스테롤, 콜산 모이어티, 폴레이트, 지질, 인지질, 바이오틴, 펜아진, 펜안트리딘, 안트라퀴논, 아다만탄, 아크리딘, 플루오레세인, 로다민, 쿠마린, 형광단, 및 염료를 포함한다.

[0327] 특정 구현예에서, 컨쥬게이트 모이어티는 활성 약물 서브스턴스, 예를 들어, 아스피린, 와파린, 페닐부타존, 이부프로펜, 수프로펜, 펜-부펜, 케토프로펜, (S)-(+)-프라노프로펜, 카프로펜, 단실사르코신, 2,3,5-트리아이오도벤조산, 핑골리모드, 플루페남산, 폴린산, 벤조티아디아자이드, 클로로티아자이드, 디아제핀, 인도-메티신, 바르비투레이트, 세팔로스포린, 설파 약물, 항당뇨병제, 항균제 또는 항생제를 포함한다.

[0328] **2. 컨쥬게이트 링커**

[0329] 컨쥬게이트 모이어티는 컨쥬게이트 링커를 통해 올리고뉴클레오타이드에 부착된다. 특정 올리고머성 화합물에서, 컨쥬게이트 링커는 단일 화학적 결합이다 (즉 컨쥬게이트 모이어티는 단일 결합을 거쳐 올리고뉴클레오타이드에 직접적으로 부착된다). 특정 구현예에서, 컨쥬게이트 링커는 사슬 구조, 예컨대 하이드로카르빌 사슬, 또는 반복 유닛 예컨대 에틸렌 글리콜, 뉴클레오사이드, 또는 아미노산 유닛의 올리고머를 포함한다.

[0330] 특정 구현예에서, 컨쥬게이트 링커는 알킬, 아미노, 옥소, 아미드, 디설파이드, 폴리에틸렌 글리콜, 에테르, 티오에테르, 및 하이드록실아미노로부터 선택된 하나 이상의 기를 포함한다. 특정 상기 구현예에서, 컨쥬게이트 링커는 알킬, 아미노, 옥소, 아미드 및 에테르 기로부터 선택된 기를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 알킬 및 아미드 기로부터 선택된 기를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 알킬 및 에테르 기로부터 선택된 기를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 적어도 하나의 인 모이어티를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 적어도 하나의 포스페이트 기를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 적어도 하나의 중성 결합기를 포함한다.

[0331] 특정 구현예에서, 상기 기재된 컨쥬게이트 링커를 포함하는, 컨쥬게이트 링커는 모 화합물, 예컨대 본 명세서에 제공된 올리고뉴클레오타이드에 컨쥬게이트 그룹 부착에 유용해지기 위해 2관능성 결합 모이어티, 예를 들면, 당해 분야에서 알려진 것들이다. 일반적으로, 2관능성 결합 모이어티는 적어도 2개의 관능성 그룹을 포함한다. 관능성 그룹 중 하나는 모 화합물 상의 특정 부위에 결합하기 위해 선택되고 다른 것은 컨쥬게이트 그룹에 결합하기 위해 선택된다. 2관능성 결합 모이어티에서 사용된 관능성 그룹의 예는 비제한적으로 친핵성 기와 반응하기 위한 친전자체 그리고 친전자성 기와 반응하기 위한 친핵체를 포함한다. 특정 구현예에서, 2관능성 결합 모이어티는 아미노, 하이드록실, 카복실산, 티올, 알킬, 알케닐, 및 알키닐로부터 선택된 하나 이상의 기를 포함한다.

[0332] 컨쥬게이트 링커의 예는 비제한적으로 피롤리딘, 8-아미노-3,6-디옥사옥탄산 (ADO), 석신이미딜 4-(N-말레이미도메틸) 사이클로헥산-1-카복실레이트 (SMCC) 및 6-아미노헥산산 (AHEX 또는 AHA)를 포함한다. 다른 컨쥬게이트 링커는 비제한적으로 치환된 또는 미치환된 C_1-C_{10} 알킬, 치환된 또는 미치환된 C_2-C_{10} 알케닐 또는 치환된 또는 미치환된 C_2-C_{10} 알키닐을 포함하고, 여기서 바람직한 치환기의 비제한 목록은 하이드록실, 아미노, 알콕시, 카복시, 벤질, 페닐, 니트로, 티올, 티오알콕시, 할로겐, 알킬, 아릴, 알케닐 및 알키닐을 포함한다.

[0333] 특정 구현예에서, 컨쥬게이트 링커는 1-10개의 링커-뉴클레오사이드를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 2-5개의 링커-뉴클레오사이드를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 정확히 3개의 링커-뉴클레오사이드를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 TCA 모티프를 포함한다. 특정 구현예에서, 그와 같은 링커-뉴클레오사이드는 변형된 뉴클레오사이드이다. 특정 구현예에서 그와 같은 링커-뉴클레오사이드는 변형된 당 모이어티를 포함한다. 특정 구현예에서, 링커-뉴클레오사이드는 미변형된다. 특정 구현예에서, 링커-뉴클레오사이드는 퓨린, 치환된 퓨린, 피리미딘 또는 치환된 피리미딘으로부터 선택된 선택적으로 보호된 복소환형 염기를 포함한다. 특정 구현예에서, 절단가능한 모이어티는 우라실, 티민, 시토신, 4-N-벤조일시토신, 5-메틸 시토신, 4-N-벤조일-5-메틸 시토신, 아데닌, 6-N-벤조일아데닌, 구아닌 및 2-N-이소부티릴구아닌으로부터 선택된 뉴클레오사이드이다. 링커-뉴클레오사이드가 표적 조직에 도달한 후 올리고머성 화합물로부터 절단되는 것이 전형적으로 바람직하다. 따라서, 링커-뉴클레오사이드는 절단가능한 결합을 통해 올리고머성 화합물의 서로에 그리고 나머지에 전형적으로 연결된다. 특정 구현예에서, 그와 같은 절단가능한 결합은 포스포디에스테르 결합이다.

[0334] 본 명세서에서, 링커-뉴클레오사이드는 올리고뉴클레오타이드의 일부인 것으로 간주되지 않는다. 따라서, 올리고머성 화합물이 참고 핵산에 명시된 퍼센트 상보성 및/또는 연결된 뉴클레오사이드의 명시된 수 또는 범위로 이루어지는 올리고뉴클레오타이드를 포함하고 올리고머성 화합물이 또한 링커-뉴클레오사이드를 포함하는 컨쥬게이트 링커를 포함하는 컨쥬게이트 그룹을 포함하는 구현예에서, 그들 링커-뉴클레오사이드는 올리고뉴클레오타이드의 길이를 대해 계수되지 않고 참고 핵산에 대하여 올리고뉴클레오타이드의 퍼센트 상보성 결정에 사용되지 않는다. 예를 들어, 올리고머성 화합물은 (1) 8-30개의 뉴클레오사이드로 이루어지는 변형된 올리고뉴클레오타이드 및 (2) 변형된 올리고뉴클레오타이드의 뉴클레오사이드로 연속인 1-10개의 링커-뉴클레오사이드를 포함하는 컨쥬게이트 그룹을 포함할 수 있다. 그와 같은 올리고머성 화합물에서 연속적 연결된 뉴클레오사이드의 총 수는 30개 초과이다. 대안적으로, 올리고머성 화합물은 8-30개의 뉴클레오사이드로 이루어지고 컨쥬게이트 그룹이 없는 변형된 올리고뉴클레오타이드를 포함할 수 있다. 그와 같은 올리고머성 화합물에서 연속적 연결된 뉴클레오사이드의 총 수는 30개 이하이다. 달리 나타내지 않는 한 컨쥬게이트 링커는 10개 이하 링커-뉴클레오사이드를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 5개 이하 링커-뉴클레오사이드를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 3개 이하 링커-뉴클레오사이드를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 2개 이하 링커-뉴클레오사이드를 포함한다. 특정 구현예에서, 컨쥬게이트 링커는 1개 이하 링커-뉴클레오사이드를 포함한다.

[0335] 특정 구현예에서, 컨쥬게이트 그룹이 올리고뉴클레오타이드로부터 절단되는 것이 바람직하다. 예를 들어, 특정 상황에서 특정 컨쥬게이트 모이어티를 포함하는 올리고머성 화합물은 특정 세포 유형에 의해 더 양호하게 차지되지만, 일단 올리고머성 화합물이 차지되면, 컨쥬게이트 그룹이 컨쥬게이션되지 않은 또는 모 올리고뉴클레오타이드를 방출시키기 위해 절단되는 것이 바람직하다. 따라서, 특정 컨쥬게이트 링커는 하나 이상의 절단가능한 모이어티를 포함할 수 있다. 특정 구현예에서, 절단가능한 모이어티는 절단가능한 결합이다. 특정 구현예에서, 절단가능한 모이어티는 적어도 하나의 절단가능한 결합을 포함하는 원자의 그룹이다. 특정 구현예에서, 절단가능한 모이어티는 1, 2, 3, 4, 또는 4개 초과 절단가능한 결합을 가지고 있는 원자의 그룹을 포함한다. 특정 구현예에서, 절단가능한 모이어티는 세포 또는 세포하 구획, 예컨대 리소좀 내부에서 선택적으로 절단된다. 특정

구현예에서, 절단가능한 모이어티는 내인성 효소, 예컨대 뉴클레아제에 의해 선택적으로 절단된다.

[0336] 특정 구현예에서, 절단가능한 결합은 하기중으로부터 선택된다: 아미드, 에스테르, 에테르, 포스포디에스테르의 한쪽 또는 양쪽 에스테르, 포스페이트 에스테르, 카바메이트, 또는 디설파이드. 특정 구현예에서, 절단가능한 결합은 포스포디에스테르의 에스테르의 한쪽 또는 양쪽이다. 특정 구현예에서, 절단가능한 모이어티는 포스페이트 또는 포스포디에스테르를 포함한다. 특정 구현예에서, 절단가능한 모이어티는 올리고뉴클레오타이드와 컨쥬게이트 모이어티 또는 컨쥬게이트 그룹 사이 포스페이트 연결기이다.

[0337] 특정 구현예에서, 절단가능한 모이어티는 하나 이상의 링커-뉴클레오사이드를 포함하거나 상기로 이루어진다. 특정 상기 구현예에서, 하나 이상의 링커-뉴클레오사이드는 절단가능한 결합을 통해 올리고머성 화합물의 서로에 및/또는 나머지에 연결된다. 특정 구현예에서, 그와 같은 절단가능한 결합은 미변형된 포스포디에스테르 결합이다. 특정 구현예에서, 절단가능한 모이어티는 포스페이트 인터뉴클레오사이드 연결기에 의해 올리고뉴클레오타이드의 3' 또는 5'-말단 뉴클레오사이드 어느 한쪽에 부착되는 그리고 포스페이트 또는 포스포로티오에이트 연결기에 의해 컨쥬게이트 링커 또는 컨쥬게이트 모이어티의 나머지에 공유적으로 부착되는 2'-데옥시 뉴클레오사이드이다. 특정 상기 구현예에서, 절단가능한 모이어티는 2'-데옥시아데노신이다.

[0338] B. 특정 말단기

[0339] 특정 구현예에서, 올리고머성 화합물은 하나 이상의 말단기를 포함한다. 특정 상기 구현예에서, 올리고머성 화합물은 안정화된 5'-포페이트를 포함한다. 안정화된 5'-포스페이트는, 비제한적으로, 5'-비닐포스포네이트를 포함하는, 비제한적으로 5'-포스파네이트를 포함한다. 특정 구현예에서, 말단기는 하나 이상의 무염기성 뉴클레오사이드 및/또는 역 뉴클레오사이드를 포함한다. 특정 구현예에서, 말단기는 하나 이상의 2'-연결된 뉴클레오사이드를 포함한다. 특정 상기 구현예에서, 2'-연결된 뉴클레오사이드는 무염기성 뉴클레오사이드이다.

[0340] III. 올리고머성 듀플렉스

[0341] 특정 구현예에서, 본 명세서에 기재된 올리고머성 화합물은, 표적 핵산의 것에 상보성인 핵염기 서열을 가지고 있는, 올리고뉴클레오타이드를 포함한다. 특정 구현예에서, 올리고머성 화합물은 올리고머성 듀플렉스를 형성하기 위해 제2 올리고머성 화합물과 짝짓기된다. 그와 같은 올리고머성 듀플렉스는 표적 핵산에 상보성인 영역을 가지고 있는 제1 올리고머성 화합물 그리고 제1 올리고머성 화합물에 상보성인 영역을 가지고 있는 제2 올리고머성 화합물을 포함한다. 특정 구현예에서, 올리고머성 듀플렉스의 제1 올리고머성 화합물은 (1) 변형된 또는 미변형된 올리고뉴클레오타이드 및 임의로 컨쥬게이트 그룹 그리고 (2) 제2 변형된 또는 미변형된 올리고뉴클레오타이드 및 임의로 컨쥬게이트 그룹을 포함하거나 상기로 이루어진다. 올리고머성 듀플렉스의 올리고머성 화합물 어느 한쪽 또는 양쪽은 컨쥬게이트 그룹을 포함할 수 있다. 올리고머성 듀플렉스의 각 올리고머성 화합물의 올리고뉴클레오타이드는 비-상보성 돌출형 뉴클레오사이드를 포함할 수 있다.

[0342] IV. 안티센스 활성

[0343] 특정 구현예에서, 올리고머성 화합물 및 올리고머성 듀플렉스는, 적어도 하나의 안티센스 활성을 초래하는, 표적 핵산에 하이브리드화할 수 있고; 그와 같은 올리고머성 화합물 및 올리고머성 듀플렉스는 안티센스 화합물이다. 특정 구현예에서, 안티센스 화합물은 이들이 표준 세포 검정에서 25% 이상만큼 표적 핵산의 양 또는 활성을 감소 또는 억제시키는 경우 안티센스 활성을 가지고 있다. 특정 구현예에서, 안티센스 화합물은 하나 이상의 표적 핵산에 선택적으로 영향을 미친다. 그와 같은 안티센스 화합물은, 하나 이상의 원하는 안티센스 활성을 초래하는, 하나 이상의 표적 핵산에 하이브리드화하는 그리고 상당한 원하지 않는 안티센스 활성을 초래하는 방식으로 하나 이상의 비-표적 핵산에 하이브리드화하지 않거나 하나 이상의 비-표적 핵산에 하이브리드화하지 않는 핵염기 서열을 포함한다.

[0344] 특정 안티센스 활성에서, 표적 핵산에 안티센스 화합물의 하이브리드화는 표적 핵산을 절단시키는 단백질의 동원을 초래한다. 예를 들어, 특정 안티센스 화합물은 표적 핵산의 RNase H 매개된 절단을 초래한다. RNase H는 RNA:DNA 듀플렉스의 RNA 가닥을 절단시키는 세포성 엔도뉴클레아제이다. 그와 같은 RNA:DNA 듀플렉스에서 DNA는 미변형된 DNA일 필요는 없다. 특정 구현예에서, RNase H 활성을 유도하기 위해 충분히 "DNA-유사"인 안티센스 화합물은 본 명세서에 기재된다. 특정 구현예에서, 갭머의 갭에서 하나 이상의 비-DNA-유사 뉴클레오사이드는 용인된다.

[0345] 특정 안티센스 활성에서, 안티센스 화합물 또는 안티센스 화합물의 일 부분은 RNA-유도된 사일런싱 복합체(RISC)에 장입되어, 궁극적으로 표적 핵산의 절단을 초래한다. 예를 들어, 특정 안티센스 화합물은 아르고노트에 의해 표적 핵산의 절단을 초래한다. RISC 속에 장입되는 안티센스 화합물은 RNAi 화합물이다. RNAi 화합물은

이중가닥 (siRNA) 또는 단일가닥 (ssRNA)일 수 있다.

[0346] 특정 구현예에서, 표적 핵산에 안티센스 화합물의 하이브리드화는 그 표적 핵산을 절단하는 단백질의 동원을 초래하지 않는다. 특정 구현예에서, 표적 핵산에 안티센스 화합물의 하이브리드화는 표적 핵산의 스플라이싱의 변경을 초래한다. 특정 구현예에서, 표적 핵산에 안티센스 화합물의 하이브리드화는 표적 핵산과 단백질 또는 다른 핵산 사이 결합 상호작용의 억제를 초래한다. 특정 구현예에서, 표적 핵산에 안티센스 화합물의 하이브리드화는 표적 핵산의 번역의 변경을 초래한다.

[0347] 안티센스 활성은 직접적으로 또는 간접적으로 관찰될 수 있다. 특정 구현예에서, 안티센스 활성의 관찰 또는 검출은 표적 핵산 또는 상기 표적 핵산에 의해 인코딩된 단백질의 양에서의 변화, 핵산 또는 단백질의 스플라이스 변이체의 비율에서의 변화 및/또는 세포 또는 동물에서 표현형 변화의 관찰 또는 검출을 포함한다.

[0348] ## V. 특정 표적 핵산

[0349] 특정 구현예에서, 올리고머성 화합물은 표적 핵산에 상보성인 영역을 포함하는 올리고뉴클레오타이드를 포함하거나 상기로 이루어진다. 특정 구현예에서, 표적 핵산은 내인성 RNA 분자이다. 특정 구현예에서, 표적 핵산은 단백질을 인코딩한다. 특정 상기 구현예에서, 표적 핵산은 하기로부터 선택된다: 인트론, 엑손 및 미번역된 영역을 포함하는, 성숙 mRNA 및 pre-mRNA. 특정 구현예에서, 표적 RNA는 성숙 mRNA이다. 특정 구현예에서, 표적 핵산은 pre-mRNA이다. 특정 상기 구현예에서, 표적 영역은 전적으로 인트론 안에 있다. 특정 구현예에서, 표적 영역은 인트론/엑손 접합을 미친다. 특정 구현예에서, 표적 영역은 인트론 내에서 적어도 50%이다. 특정 구현예에서, 표적 핵산은 레트로진의 RNA 전사적 산물이다. 특정 구현예에서, 표적 핵산은 비-코딩 RNA이다. 특정 상기 구현예에서, 표적 비-코딩 RNA는 하기로부터 선택된다: 긴 비-코딩 RNA, 짧은 비-코딩 RNA, 인트론 RNA 분자.

[0350] ### A. 표적 핵산에 대한 상보성/미스매치

[0351] 활성 제거 없이 미스매치 염기를 도입하는 것은 가능하다. 예를 들어, Gautschi 등 (J. Natl. Cancer Inst. 93:463-471, March 2001)은 시험관내 및 생체내 bcl-2 및 bcl-xL 둘 모두의 발현을 감소시키기 위해 bcl-xL mRNA에 3개의 미스매치를 가지고 있는 그리고 bcl-2 mRNA에 100% 상보성을 가지고 있는 올리고뉴클레오타이드의 활성을 증명하였다. 게다가, 이 올리고뉴클레오타이드는 생체내 잠재적 항-종양 활성을 증명하였다. Maher 및 Dolnick (Nuc. Acid. Res. 16:3341-3358, 1988)은, 토끼 망상적혈구 검정에서 인간 DHFR의 번역을 정지시키기 위한 그들의 능력에 대하여, 2 또는 3개의 탬덤 올리고뉴클레오타이드의 서열, 각각으로 구성된 28 및 42개 핵염기 올리고뉴클레오타이드, 그리고 탠덤 14개 핵염기 올리고뉴클레오타이드의 시리즈를 시험하였다. 각 3개의 14개 핵염기 올리고뉴클레오타이드 단독은 28 또는 42개 핵염기 올리고뉴클레오타이드보다 더 많은 적절한 수준에서이지만, 번역을 억제시킬 수 있었다.

[0352] 특정 구현예에서, 올리고뉴클레오타이드는 올리고뉴클레오타이드의 전체 길이에 걸쳐 표적 핵산에 상보성이다. 특정 구현예에서, 올리고뉴클레오타이드는 표적 핵산에 99%, 95%, 90%, 85%, 또는 80% 상보성이다. 특정 구현예에서, 올리고뉴클레오타이드는 올리고뉴클레오타이드의 전체 길이에 걸쳐 표적 핵산에 적어도 80% 상보성이고 표적 핵산에 100% 또는 완전하게 상보성인 영역을 포함한다. 특정 구현예에서, 완전한 상보성의 영역은 6 내지 20, 10 내지 18, 또는 18 내지 20개 핵염기 길이이다.

[0353] 특정 구현예에서, 올리고뉴클레오타이드는 표적 핵산에 비하여 하나 이상의 미스매치된 핵염기를 포함한다. 특정 구현예에서, 표적에 대한 안티센스 활성은 그와 같은 미스매치만큼 감소되지만, 비-표적에 대한 활성은 더 큰 양만큼 감소된다. 따라서, 특정 구현예에서 올리고뉴클레오타이드의 선택성은 개선된다. 특정 구현예에서, 미스매치는 갭머 모티프를 가지고 있는 올리고뉴클레오타이드 내에서 특이적으로 위치한다. 특정 구현예에서, 미스매치는 갭 영역의 5'-말단으로부터 1, 2, 3, 4, 5, 6, 7, 또는 8번 위치에 있다. 특정 구현예에서, 미스매치는 갭 영역의 3'-말단으로부터 9, 8, 7, 6, 5, 4, 3, 2, 1번 위치에 있다. 특정 구현예에서, 미스매치는 윙 영역의 5'-말단으로부터 1, 2, 3, 또는 4번 위치에 있다. 특정 구현예에서, 미스매치는 윙 영역의 3'-말단으로부터 4, 3, 2, 또는 1번 위치에 있다.

[0354] ### B. LRRK2

[0355] 특정 구현예에서, 올리고머성 화합물은 표적 핵산에 상보성인 영역을 포함하는 올리고뉴클레오타이드를 포함하거나 상기로 이루어지고, 여기서 상기 표적 핵산은 LRRK2이다. 특정 구현예에서, LRRK2 핵산은 서열번호: 1 (유전자은행 기탁 번호: NM_198578.3) 및 서열번호: 2 (뉴클레오타이드 2759000 내지 2909000으로부터 절단된 유전

자은행 기탁 번호 : NT_029419.11)에서 제시된 서열을 가지고 있다.

[0356] 특정 구현예에서, 서열번호: 1 또는 서열번호: 2에 상보성인 올리고머성 화합물과 세포의 접촉은 LRRK2 RNA의 양을 감소시키고, 특정 구현예에서 LRRK2 단백질의 양을 감소시킨다. 특정 구현예에서, 올리고머성 화합물은 변형된 올리고뉴클레오타이드로 이루어진다. 특정 구현예에서, 서열번호: 1 또는 서열번호: 2에 상보성인 올리고머성 화합물과 세포의 접촉은 신경퇴행성 질환의 하나 이상의 징후 또는 특징을 개선한다. 특정 구현예에서, 올리고머성 화합물은 변형된 올리고뉴클레오타이드로 이루어진다. 특정 구현예에서, 징후 또는 특징은 운동실조증, 신경병증, 및 응집체 형성이다. 특정 구현예에서, 서열번호: 1 또는 서열번호: 2에 상보성인 변형된 올리고뉴클레오타이드와 세포의 접촉은 개선된 운동 기능, 감소된 신경병증, 및 응집체의 수에서의 감소를 초래한다. 특정 구현예에서, 올리고머성 화합물은 변형된 올리고뉴클레오타이드로 이루어진다.

[0357] C. 특정 조직내 특정 표적 핵산

[0358] 특정 구현예에서, 올리고머성 화합물은 표적 핵산에 상보성인 영역을 포함하는 올리고뉴클레오타이드를 포함하거나 상기로 이루어지고, 여기서 상기 표적 핵산은 약리학적으로 관련 조직에서 발현된다. 특정 구현예에서, 약리학적으로 관련 조직은 중추 신경계 (CNS)를 포함하는 조직 및 세포이다. 그와 같은 조직은 뇌조직, 예컨대, 대뇌피질, 흑질, 선조체, 중뇌, 및 뇌간 그리고 척수를 포함한다.

[0359] VI. 특정 약제학적 조성물

[0360] 특정 구현예에서, 하나 이상의 올리고머성 화합물을 포함하는 약제학적 조성물은 본 명세서에 기재된다. 특정 구현예에서, 하나 이상의 올리고머성 화합물 각각은 변형된 올리고뉴클레오타이드로 이루어진다. 특정 구현예에서, 약제학적 조성물은 약제학적으로 허용가능한 희석제 또는 담체를 포함한다. 특정 구현예에서, 약제학적 조성물은 멸균 염수 용액 및 하나 이상의 올리고머성 화합물을 포함하거나 상기로 이루어진다. 특정 구현예에서, 멸균 염수는 약제학적 등급 염수이다. 특정 구현예에서, 약제학적 조성물은 하나 이상의 올리고머성 화합물 및 멸균수를 포함하거나 상기로 이루어진다. 특정 구현예에서, 멸균수는 약품 등급 물이다. 특정 구현예에서, 약제학적 조성물은 하나 이상의 올리고머성 화합물 및 포스페이트-완충 염수 (PBS)를 포함하거나 상기로 이루어진다. 특정 구현예에서, 멸균 PBS는 약품 등급 PBS이다. 특정 구현예에서, 약제학적 조성물은 하나 이상의 올리고머성 화합물 및 인공 뇌척수액을 포함하거나 상기로 이루어진다. 특정 구현예에서, 인공 뇌척수액은 약품 등급이다.

[0361] 특정 구현예에서, 약제학적 조성물은 변형된 올리고뉴클레오타이드 및 인공 뇌척수액을 포함한다. 특정 구현예에서, 약제학적 조성물은 변형된 올리고뉴클레오타이드 및 인공 뇌척수액으로 이루어진다. 특정 구현예에서, 약제학적 조성물은 본질적으로 변형된 올리고뉴클레오타이드 및 인공 뇌척수액으로 이루어진다. 특정 구현예에서, 인공 뇌척수액은 약품 등급이다.

[0362] 특정 구현예에서, 약제학적 조성물은 하나 이상의 올리고머성 화합물 및 하나 이상의 부형제를 포함한다. 특정 구현예에서, 부형제는 물, 염 용액, 알코올, 폴리에틸렌 글리콜, 젤라틴, 락토스, 아밀라제, 스테아르산마그네슘, 탈크, 규산, 점성 파라핀, 하이드록시메틸셀룰로스 및 폴리비닐피롤리돈으로부터 선택된다.

[0363] 특정 구현예에서, 올리고머성 화합물은 약제학적 조성물 또는 제형의 제조를 위하여 약제학적으로 허용가능한 활성 및/또는 불활성 서브스턴스와 혼합될 수 있다. 조성물 및 약제학적 조성물의 제형화 방법은, 비제한적으로, 투여의 경로, 질환의 정도, 또는 투여되어야 하는 용량을 포함하여, 다수의 기준에 의존한다.

[0364] 특정 구현예에서, 올리고머성 화합물을 포함하는 약제학적 조성물은 올리고머성 화합물의 임의의 약제학적으로 허용가능한 염, 올리고머성 화합물의 에스테르, 또는 상기 에스테르의 염을 포괄한다. 특정 구현예에서, 인간을 포함하는, 동물에 투여시, 하나 이상의 올리고뉴클레오타이드를 포함하는 올리고머성 화합물을 포함하는 약제학적 조성물은 생물학적으로 활성 대사물질 또는 이의 잔여물을 (직접적으로 또는 간접적으로) 제공할 수 있다. 따라서, 예를 들어, 본 개시내용은 또한 올리고머성 화합물의 약제학적으로 허용가능한 염, 전구약물, 상기 전구약물의 약제학적으로 허용가능한 염, 및 기타 생물동등물로 그려진다. 적당한 약제학적으로 허용가능한 염은, 비제한적으로, 나트륨 및 칼륨 염을 포함한다. 특정 구현예에서, 전구약물은 올리고뉴클레오타이드에 부착된 하나 이상의 컨쥬게이트 그룹을 포함하고, 여기서 상기 컨쥬게이트 그룹은 바디 내에서 내인성 뉴클레아제에 의해 절단된다.

[0365] 지질 모이어티는 다양한 방법에서 핵산 요법에 사용되어 왔다. 특정 상기 방법에서, 핵산, 예컨대 올리고머성 화합물은 양이온성 지질 및 중성 지질의 혼합물로 만들어진 사전형성된 리포좀 또는 리포플렉스 속에 도입된다. 특정 방법에서, 모노- 또는 폴리-양이온성 지질을 가진 DNA 복합체는 중성 지질의 존재 없이 형성된다. 특정 구

현예에서, 지질 모이어티는 특정 세포 또는 조직에 약제학적 제제의 분포를 증가시키도록 선택된다. 특정 구현예에서, 지질 모이어티는 지방 조직에 약제학적 제제의 분포를 증가시키도록 선택된다. 특정 구현예에서, 지질 모이어티는 근육 조직에 약제학적 제제의 분포를 증가시키도록 선택된다.

[0366] 특정 구현예에서, 약제학적 조성물은 전달 시스템을 포함한다. 전달 시스템의 예는, 비제한적으로, 리포좀 또는 유탁액을 포함한다. 특정 전달 시스템은 소수성 화합물을 포함하는 것을 포함하는 특정 약제학적 조성물 제조에 유용하다. 특정 구현예에서, 특정 유기 용매 예컨대 디메틸설폭사이드는 사용된다.

[0367] 특정 구현예에서, 약제학적 조성물은 특이적 조직 또는 세포 유형에 본 발명의 하나 이상의 약제학적 제제를 전달하도록 설계된 하나 이상의 조직-특이적 전달 분자를 포함한다. 예를 들어, 특정 구현예에서, 약제학적 조성물은 조직-특이적 항체로 코팅된 리포좀을 포함한다.

[0368] 특정 구현예에서, 약제학적 조성물은 공-용매 시스템을 포함한다. 특정한 상기 공-용매 시스템은, 예를 들어, 벤질 알코올, 무극성 계면활성, 수혼화성 유기 폴리머, 및 수상을 포함한다. 특정 구현예에서, 상기 공-용매 시스템은 소수성 화합물에 사용된다. 상기 공-용매 시스템의 비-제한 예는 VPD 공-용매 시스템이고, 이는 3% w/v 벤질 알코올, 8% w/v의 무극성 계면활성제 Polysorbate 80™ 및 65% w/v 폴리에틸렌 글리콜 300을 포함하는 무수 에탄올의 용액이다. 상기 공-용매 시스템의 분율은 그들의 용해성 및 독성 특성의 유의미한 변경 없이 상당히 다양할 수 있다. 게다가, 공-용매 성분의 정체성은 다양할 수 있다: 예를 들어, 다른 계면활성제는 Polysorbate 80™ 대신 사용될 수 있고; 폴리에틸렌 글리콜의 분획 크기는 다양할 수 있고; 다른 생물적합성 폴리머는 폴리에틸렌 글리콜, 예를 들면, 폴리비닐 피롤리돈을 대체할 수 있고; 다른 당 또는 폴리사카라이드는 덱스트로스를 대신할 수 있다.

[0369] 특정 구현예에서, 약제학적 조성물은 경구 투여를 위하여 제조된다. 특정 구현예에서, 약제학적 조성물은 구강 투여를 위하여 제조된다. 특정 구현예에서, 약제학적 조성물은 주사로 (예를 들면, 정맥내, 피하, 근육내, 척추강내 (IT), 뇌실내 (ICV), 등) 투여를 위하여 제조된다. 특정한 상기 구현예에서, 약제학적 조성물은 담체를 포함하고 수용액, 예컨대 물 또는 생리학적으로 상용성 완충액 예컨대 항크스액, 링거액, 또는 생리학적 염수 완충액에서 제형화된다. 특정 구현예에서, 다른 재료 (예를 들면, 용해성을 돕거나 보존제로서 작용하는 재료)는 포함된다. 특정 구현예에서, 주사가능한 현탁액은 적당한 액체 담체, 현탁제 및 기타 등등을 사용하여 제조된다. 주사용 특정 약제학적 조성물은 단위 투약량 형태, 예를 들면, 앰풀 또는 다-용량 컨테이너로 제시된다. 주사용 특정 약제학적 조성물은 유성 또는 수성 비히클에서 현탁액, 용액 또는 유탁액이고, 제형성 제제 예컨대 현탁제, 안정화제 및/또는 분산제를 함유할 수 있다. 주사용 약제학적 조성물에서 사용에 적당한 특정 용매는, 비제한적으로, 친유성 용매 및 지방 오일, 예컨대 참깨 오일, 합성 지방산 에스테르, 예컨대 에틸 올레에이트 또는 트리글리세라이드, 및 리포좀을 포함한다.

[0370] 특정 조건 하에서, 본 명세서에 개시된 특정 화합물은 산으로서 작용한다. 그와 같은 화합물이 양성화된 (자유산) 형태로, 이온화된 (음이온) 형태로, 또는 이온화되고 양이온 (염) 형태와 회합으로 그려질 수 있거나 기재될 수 있어도, 그와 같은 화합물의 수용액은 그와 같은 형태 중에서 평형상태로 실존한다. 예를 들어, 수용액내 올리고뉴클레오타이드의 포스페이트 연결기는 자유 산, 음이온, 및 염 형태 중에서 평형상태로 실존한다. 달리 나타내지 않는 한, 본 명세서에 기재된 화합물은 모든 그와 같은 형태를 포함하기 위한 것이다. 더욱이, 특정 올리고뉴클레오타이드는 몇몇 그와 같은 연결기를 가지고 있고, 이들 각각은 평형상태이다. 따라서, 용액내 올리고뉴클레오타이드는 평형상태로 다중 위치 모두에서 형태의 앙상블로 실존한다. 용어 "올리고뉴클레오타이드"는 모든 그와 같은 형태를 포함하기 위한 것이다. 작도된 구조는 반드시 단일 형태를 묘사한다. 그럼에도 불구하고, 달리 나타내지 않는 한, 그와 같은 도면은 마찬가지로 상응하는 형태를 포함하기 위한 것이다. 본 명세서에, 용어 "또는 이의 염"이 뒤따르는 화합물의 자유 산을 묘사하는 구조는 완전하게 또는 부분적으로 양성화/탈-양성화/양이온과 회합될 수 있는 모든 그와 같은 형태를 명백히 포함한다. 특정 사례에서, 하나 이상의 구체적 양이온은 확인된다.

[0371] 특정 구현예에서, 본 명세서에 개시된 올리고머성 화합물은 나트륨을 가진 수용액에 있다. 특정 구현예에서, 올리고머성 화합물은 칼륨을 가진 수용액에 있다. 특정 구현예에서, 올리고머성 화합물은 인위적 CSF에 있다. 특정 구현예에서, 올리고머성 화합물은 PBS에 있다. 특정 구현예에서, 올리고머성 화합물은 물에 있다. 특정 상기 구현예에서, 용액의 pH는 원하는 pH를 달성하기 위해 NaOH 및/또는 HCl로 조정된다.

[0372] **VII. 특정 조성물**

[0373] 1. 화합물 번호: 780241

[0374] 화합물 번호: 780241은, (서열번호: 222로서 본 명세서에 편입된) (5'부터 3'까지) GCTCATATCTAAAGACCGCA의 서열을 가지고 있는, 5-10-5 MOE 갭머로서 특성규명될 수 있고, 여기서 각각의 뉴클레오사이드 1-5 및 16-20 (5'부터 3'까지)는 2'-MOE 변형을 포함하고 각각의 뉴클레오사이드 6-15는 2'-데옥시뉴클레오사이드이고, 여기서 뉴클레오사이드 2 내지 3, 3 내지 4, 4 내지 5, 16 내지 17, 및 17 내지 18 사이 인터뉴클레오사이드 연결기는 포스포디에스테르 인터뉴클레오사이드 연결기이고 뉴클레오사이드 1 내지 2, 5 내지 6, 6 내지 7, 7 내지 8, 8 내지 9, 9 내지 10, 10 내지 11, 11 내지 12, 12 내지 13, 13 내지 14, 14 내지 15, 15 내지 16, 18 내지 19, 및 19 내지 20 사이 인터뉴클레오사이드 연결기는 포스포로티오에이트 인터뉴클레오사이드 연결기이고, 상기 각 시토신은 5-메틸 시토신이다.

[0375] 화합물 번호: 780241은 하기 화학 표기법으로 특성규명될 수 있다: Ges mCeo Teo mCeo Aes Tds Ads Tds mCds Tds Ads Ads Ads Gds Ads mCeo mCeo Ges mCes Ae; 여기서,

[0376] A = 아데닌 핵염기,

[0377] mC = 5-메틸 시토신 핵염기,

[0378] G = 구아닌 핵염기,

[0379] T = 티민 핵염기,

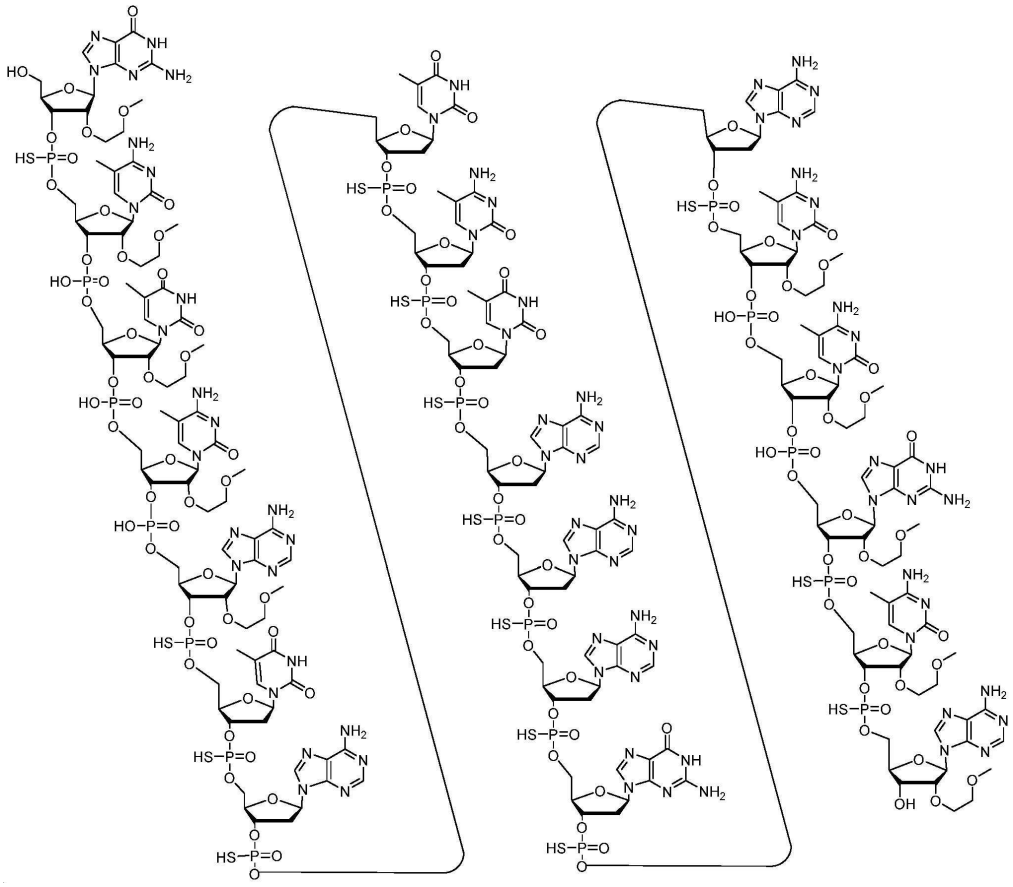
[0380] e = 2'-MOE 변형된 당,

[0381] d = 2'-데옥시리보오스 당,

[0382] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

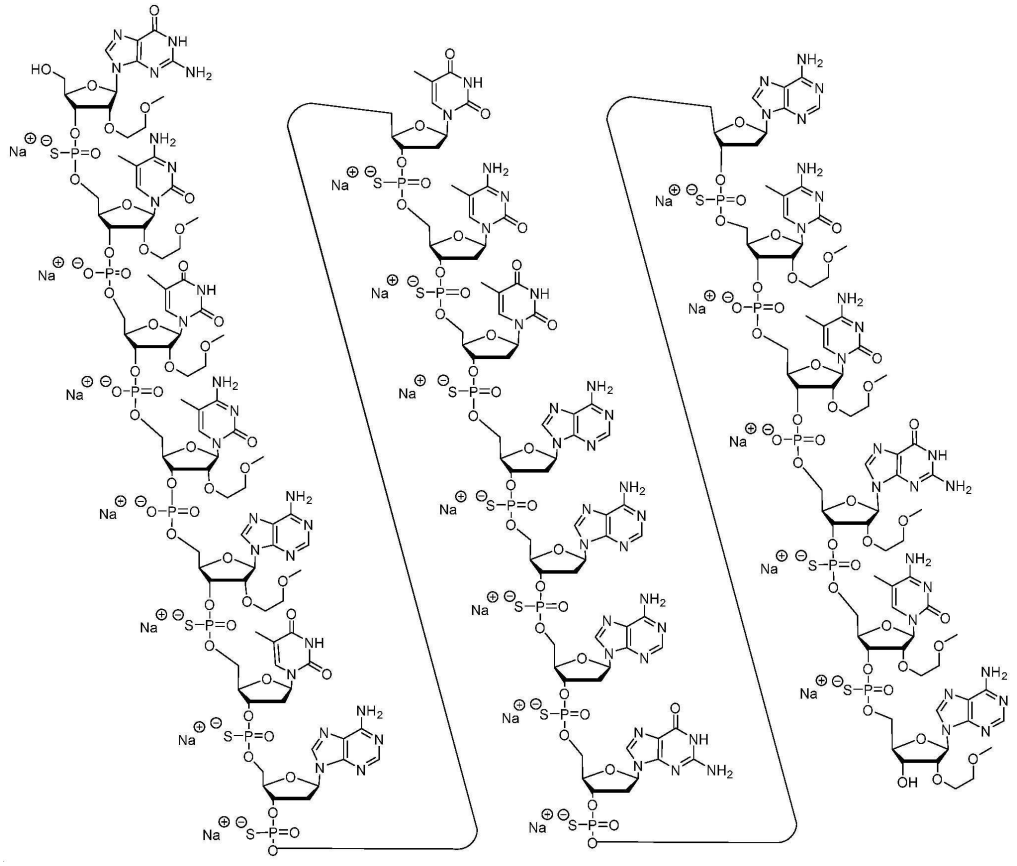
[0383] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

[0384] 화합물 번호: 780241은 하기 화학 구조로 나타낼 수 있다:

[0385] 

[0386] **구조 1. 화합물 번호: 780241** (서열번호: 222).

[0387] 화합물 번호: 780241은 하기 화학 구조로 나타낼 수 있다:



[0388]

[0389] **구조 2. 화합물 번호: 780241의 나트륨 염** (서열번호: 222).

[0390] 2. 화합물 번호: 802714

[0391] 화합물 번호: 802714는, (서열번호: 888로서 본 명세서에 편입된) (5'부터 3'까지) TCACCACAAACTCATGGACT의 서열을 가지고 있는, 5-10-5 MOE 갭머로서 특성규명될 수 있고, 여기서 각각의 뉴클레오사이드 1-5 및 16-20 (5'부터 3'까지)는 2'-MOE 변형을 포함하고 각각의 뉴클레오사이드 6-15는 2'-데옥시뉴클레오사이드이고, 여기서 뉴클레오사이드 2 내지 3, 3 내지 4, 4 내지 5, 16 내지 17, 및 17 내지 18 사이 인터뉴클레오사이드 연결기는 포스포디에스테르 인터뉴클레오사이드 연결기이고 뉴클레오사이드 1 내지 2, 5 내지 6, 6 내지 7, 7 내지 8, 8 내지 9, 9 내지 10, 10 내지 11, 11 내지 12, 12 내지 13, 13 내지 14, 14 내지 15, 15 내지 16, 18 내지 19, 및 19 내지 20 사이 인터뉴클레오사이드 연결기는 포스포로티오에이트 인터뉴클레오사이드 연결기이고, 상기 각 시토신은 5-메틸 시토신이다.

[0392] 화합물 번호: 802714는 하기 화학 표기법으로 특성규명될 수 있다: Tes mCeo Aeo mCeo mCes Ads mCds Ads Ads Ads mCds Tds mCds Ads Tds Geo Geo Aes mCes Te; 여기서,

[0393] A = 아데닌 핵염기,

[0394] mC = 5-메틸 시토신 핵염기,

[0395] G = 구아닌 핵염기,

[0396] T = 티민 핵염기,

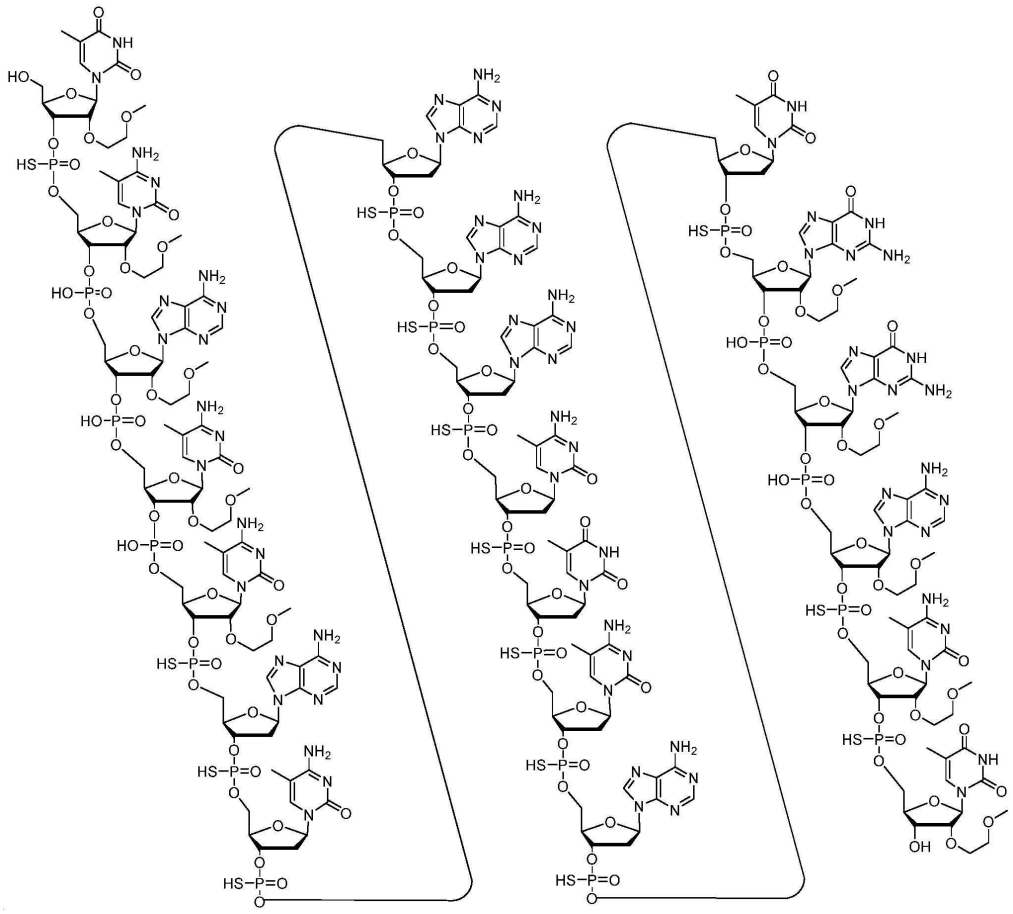
[0397] e = 2'-MOE 변형된 당,

[0398] d = 2'-데옥시리보오스 당,

[0399] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

[0400] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

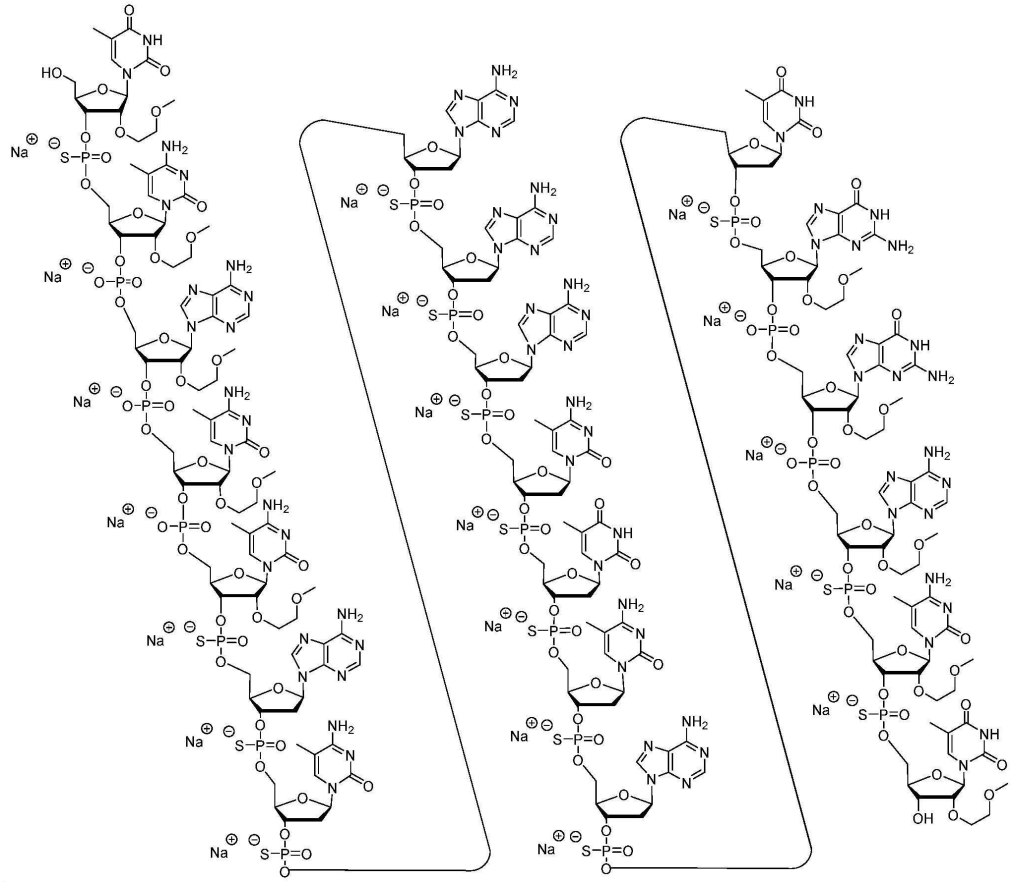
[0401] 화합물 번호: 802714는 하기 화학 구조로 나타낼 수 있다:



[0402]

[0403] **구조 3. 화합물 번호: 802714** (서열번호: 888).

[0404] 화합물 번호: 802714는 하기 화학 구조로 나타낼 수 있다:



[0405]

[0406] **구조 4. 화합물 번호: 802714의 나트륨 염** (서열번호: 888).

[0407] 3. 화합물 번호: 803268

[0408] 화합물 번호: 803268은, (서열번호: 1431로서 본 명세서에 편입된) (5'부터 3'까지) ACCCTTTCCATGTGAACATT의 서열을 가지고 있는, 5-10-5 MOE 갭머로서 특성규명될 수 있고, 여기서 각각의 뉴클레오사이드 1-5 및 16-20 (5'부터 3'까지)는 2'-MOE 변형을 포함하고 각각의 뉴클레오사이드 6-15는 2'-데옥시뉴클레오사이드이고, 여기서 뉴클레오사이드 2 내지 3, 3 내지 4, 4 내지 5, 16 내지 17, 및 17 내지 18 사이 인터뉴클레오사이드 연결기는 포스포디에스테르 인터뉴클레오사이드 연결기이고 뉴클레오사이드 1 내지 2, 5 내지 6, 6 내지 7, 7 내지 8, 8 내지 9, 9 내지 10, 10 내지 11, 11 내지 12, 12 내지 13, 13 내지 14, 14 내지 15, 15 내지 16, 18 내지 19, 및 19 내지 20 사이 인터뉴클레오사이드 연결기는 포스포로티오에이트 인터뉴클레오사이드 연결기이고, 상기 각 시토신은 5-메틸 시토신이다.

[0409] 화합물 번호: 803268은 하기 화학 표기법으로 특성규명될 수 있다: Aes mCeo mCeo mCeo Tes Tds Tds mCds mCds Ads Tds Gds Tds Gds Ads Aeo mCeo Aes Tes Te; 여기서,

[0410] A = 아데닌 핵염기,

[0411] mC = 5-메틸 시토신 핵염기,

[0412] G = 구아닌 핵염기,

[0413] T = 티민 핵염기,

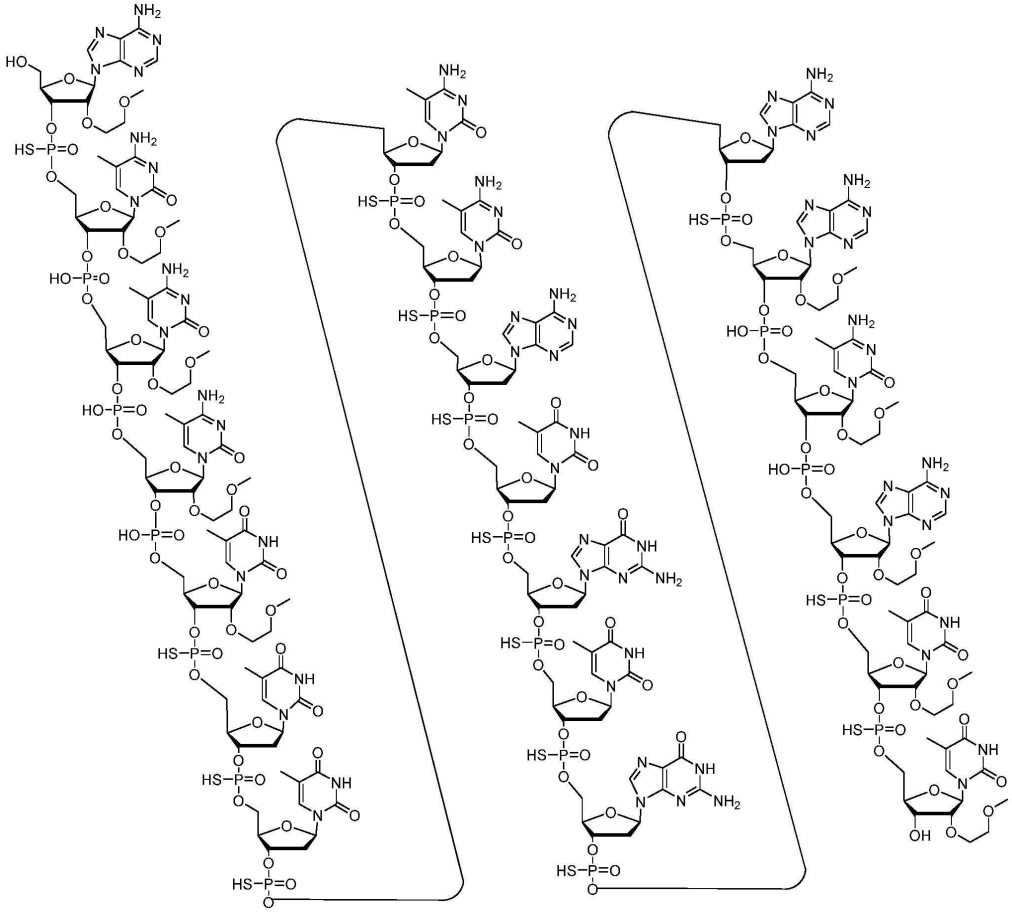
[0414] e = 2'-MOE 변형된 당,

[0415] d = 2'-데옥시리보오스 당,

[0416] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

[0417] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

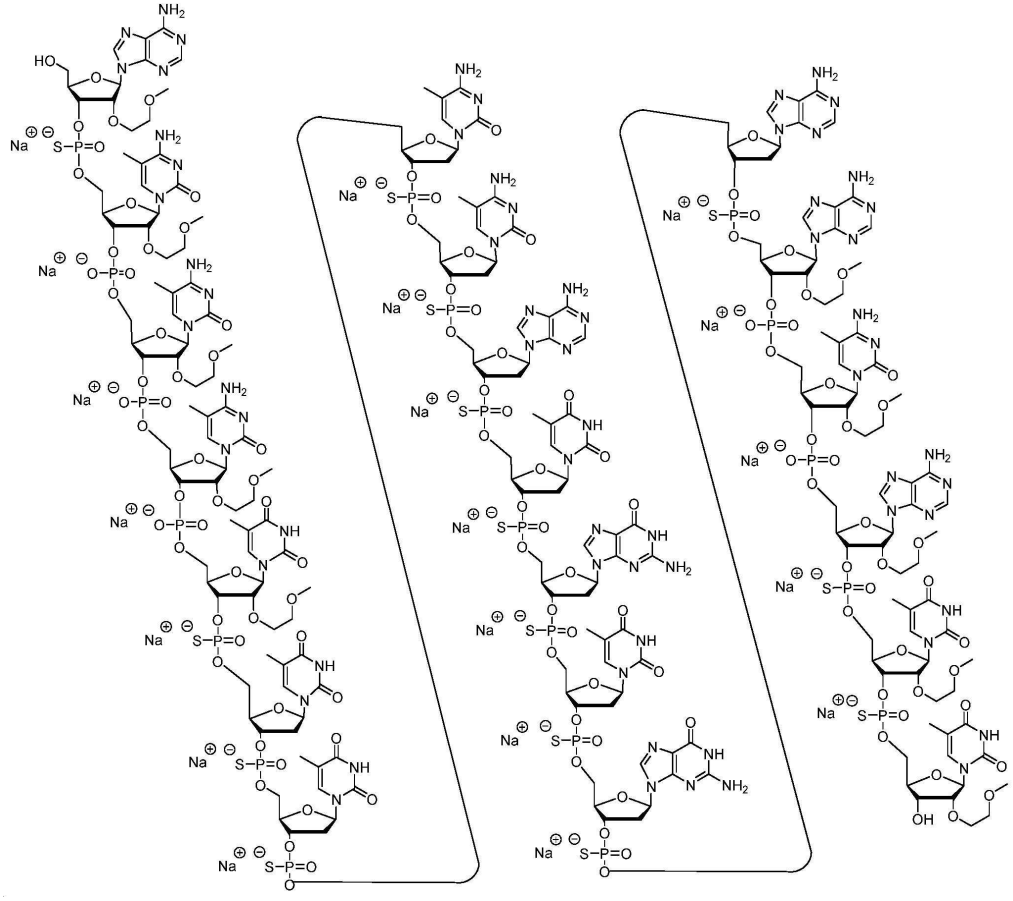
[0418] 화합물 번호: 803268은 하기 화학 구조로 나타낼 수 있다:



[0419]

[0420] **구조 5. 화합물 번호: 803268** (서열번호: 1431).

[0421] 화합물 번호: 803268은 하기 화학 구조로 나타낼 수 있다:



[0422]

[0423] **구조 6. 화합물 번호: 803268의 나트륨 염** (서열번호: 1431).

[0424] 4. 화합물 번호: 876031

[0425] 화합물 번호: 876031은, (서열번호: 3590으로서 본 명세서에 편입된) (5'부터 3'까지) ACGCACTTAACAATATCATA의 서열을 가지고 있는, 5-10-5 MOE 갭머로서 특성규명될 수 있고, 여기서 각각의 뉴클레오사이드 1-5 및 16-20 (5'부터 3'까지)는 2'-MOE 변형을 포함하고 각각의 뉴클레오사이드 6-15는 2'-데옥시뉴클레오사이드이고, 여기서 뉴클레오사이드 2 내지 3, 3 내지 4, 4 내지 5, 16 내지 17, 및 17 내지 18 사이 인터뉴클레오사이드 연결기는 포스포디에스테르 인터뉴클레오사이드 연결기이고 뉴클레오사이드 1 내지 2, 5 내지 6, 6 내지 7, 7 내지 8, 8 내지 9, 9 내지 10, 10 내지 11, 11 내지 12, 12 내지 13, 13 내지 14, 14 내지 15, 15 내지 16, 18 내지 19, 및 19 내지 20 사이 인터뉴클레오사이드 연결기는 포스포로티오에이트 인터뉴클레오사이드 연결기이고, 상기 각 시토신은 5-메틸 시토신이다.

[0426] 화합물 번호: 876031은 하기 화학 표기법으로 특성규명될 수 있다: Aes mCeo Geo mCeo Aes mCds Tds Tds Ads Ads mCds Ads Ads Tds Ads Teo mCeo Aes Tes Ae; 여기서,

[0427] A = 아데닌 핵염기,

[0428] mC = 5-메틸 시토신 핵염기,

[0429] G = 구아닌 핵염기,

[0430] T = 티민 핵염기,

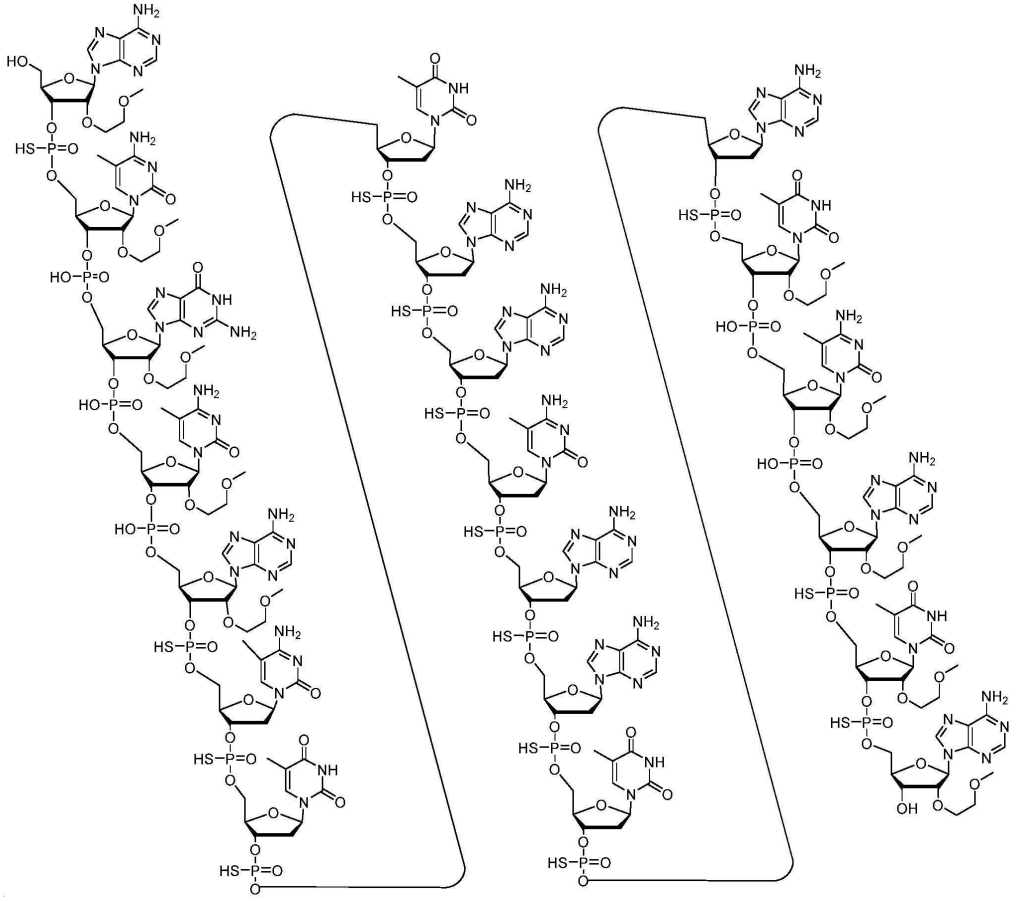
[0431] e = 2'-MOE 변형된 당,

[0432] d = 2'-데옥시리보오스 당,

[0433] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

[0434] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

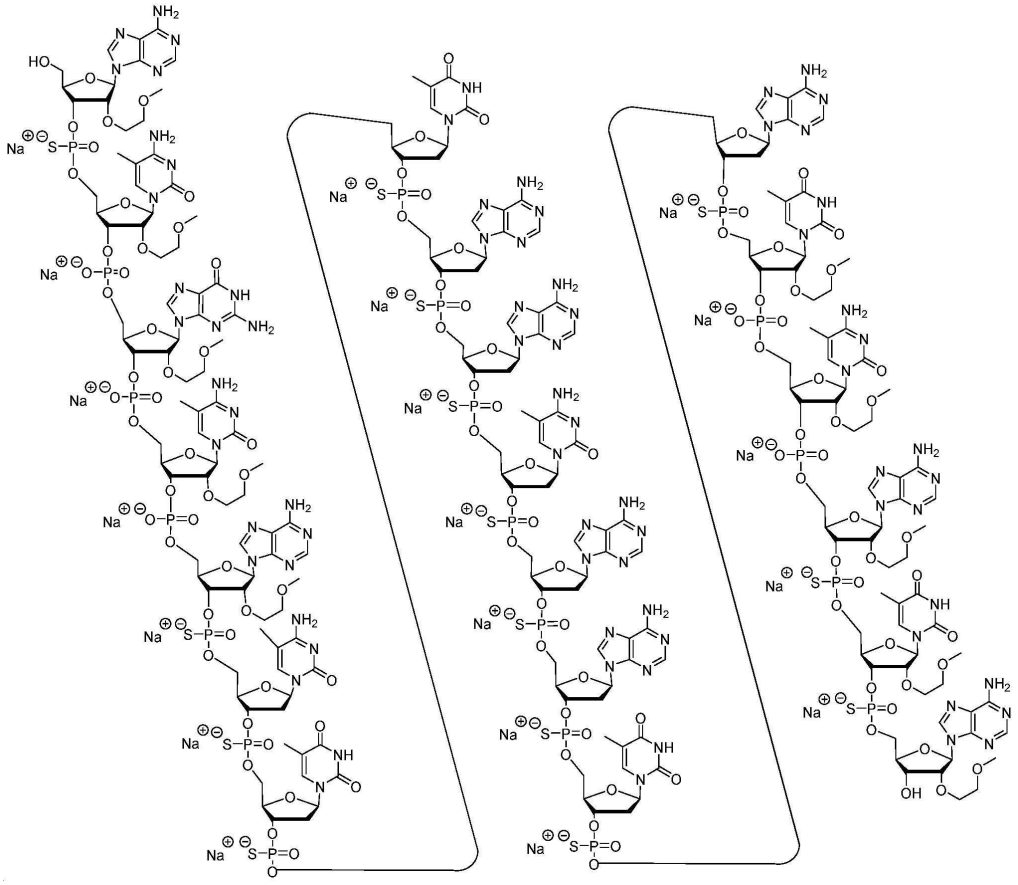
[0435] 화합물 번호: 876031은 하기 화학 구조로 나타낼 수 있다:



[0436]

[0437] **구조 7. 화합물 번호: 876031** (서열번호: 3590).

[0438] 화합물 번호: 876031은 하기 화학 구조로 나타낼 수 있다:



[0439]

[0440] **구조 8. 화합물 번호: 876031의 나트륨 염** (서열번호: 3590).

[0441] 5. 화합물 번호: 876604

[0442] 화합물 번호: 876604는, (서열번호: 3385로서 본 명세서에 편입된) (5'부터 3'까지) AGCAATCATTGGTAGCATAC의 서열을 가지고 있는, 5-10-5 MOE 갭머로서 특성규명될 수 있고, 여기서 각각의 뉴클레오사이드 1-5 및 16-20 (5'부터 3'까지)는 2'-MOE 변형을 포함하고 각각의 뉴클레오사이드 6-15는 2'-데옥시뉴클레오사이드이고, 여기서 뉴클레오사이드 2 내지 3, 3 내지 4, 4 내지 5, 16 내지 17, 및 17 내지 18 사이 인터뉴클레오사이드 연결기는 포스포디에스테르 인터뉴클레오사이드 연결기이고 뉴클레오사이드 1 내지 2, 5 내지 6, 6 내지 7, 7 내지 8, 8 내지 9, 9 내지 10, 10 내지 11, 11 내지 12, 12 내지 13, 13 내지 14, 14 내지 15, 15 내지 16, 18 내지 19, 및 19 내지 20 사이 인터뉴클레오사이드 연결기는 포스포로티오에이트 인터뉴클레오사이드 연결기이고, 상기 각 시토신은 5-메틸 시토신이다.

[0443] 화합물 번호: 876604는 하기 화학 표기법으로 특성규명될 수 있다: Aes Geo mCeo Aeo Aes Tds mCds Ads Tds Tds Gds Gds Tds Ads Gds mCeo Aeo Tes Aes mCe; 여기서,

[0444] A = 아데닌 핵염기,

[0445] mC = 5-메틸 시토신 핵염기,

[0446] G = 구아닌 핵염기,

[0447] T = 티민 핵염기,

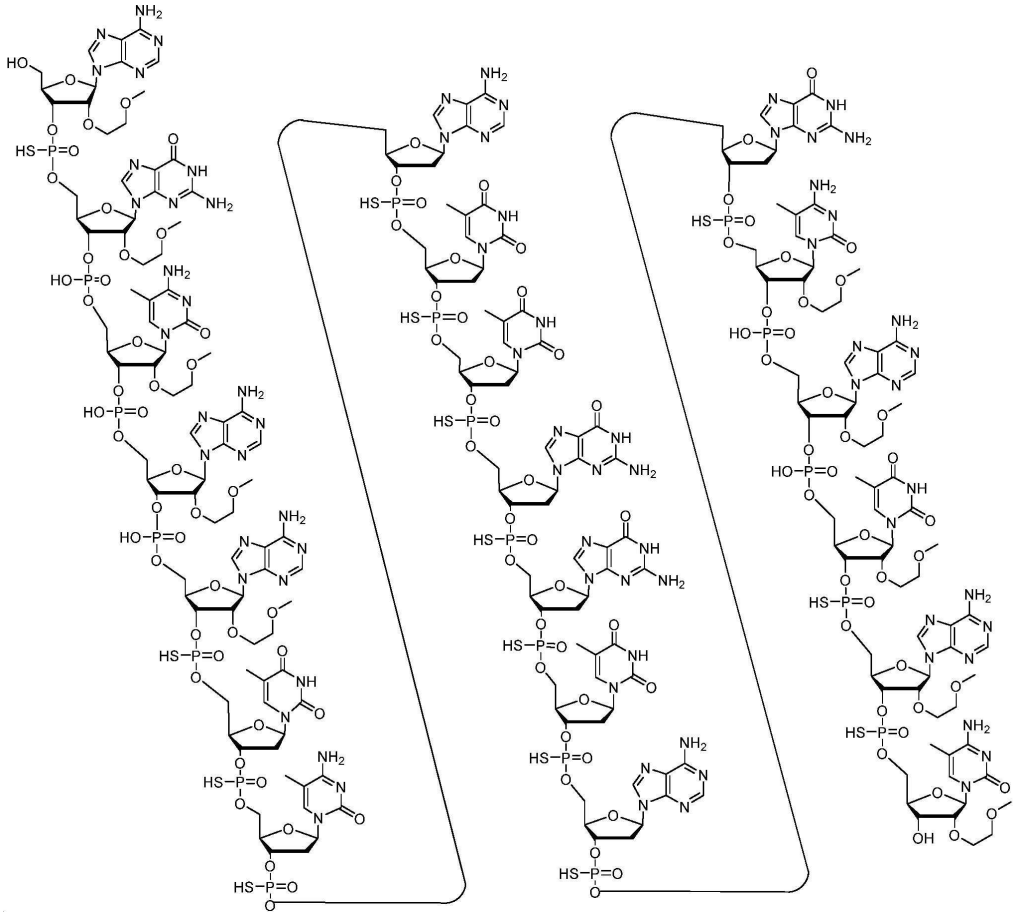
[0448] e = 2'-MOE 변형된 당,

[0449] d = 2'-데옥시리보오스 당,

[0450] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

[0451] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

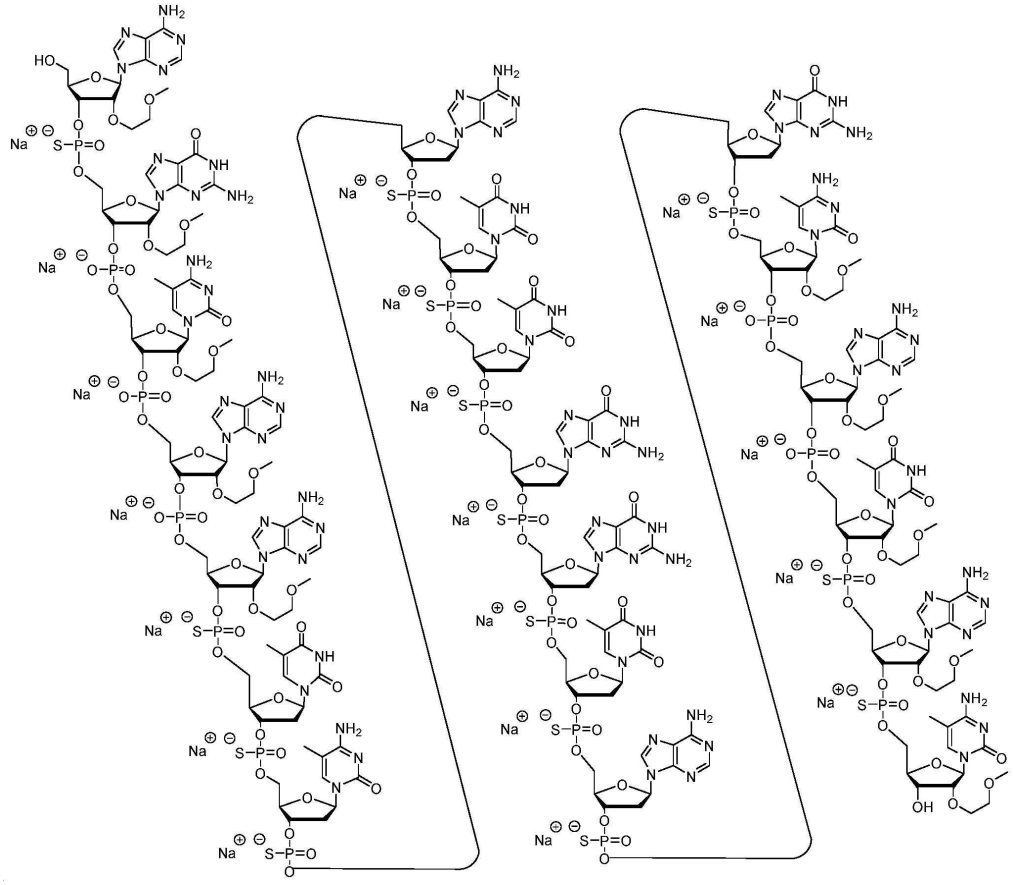
[0452] 화합물 번호: 876604는 하기 화학 구조로 나타낼 수 있다:



[0453]

[0454] **구조 8. 화합물 번호: 876604** (서열번호: 3385).

[0455] 화합물 번호: 876604는 하기 화학 구조로 나타낼 수 있다:



[0456]

[0457] **구조 10. 화합물 번호: 876604의 나트륨 염** (서열번호: 3385).

[0458] 6. 화합물 번호: 934556

[0459] 화합물 번호: 934556은, (서열번호: 852로서 본 명세서에 편입된) (5'부터 3'까지) CGCACTTAACAATATCATAT의 서열을 가지고 있는, 5-10-5 MOE 갭머로서 특성규명될 수 있고, 여기서 각각의 뉴클레오사이드 1-5 및 16-20 (5'부터 3'까지)는 2'-MOE 변형을 포함하고 각각의 뉴클레오사이드 6-15는 2'-데옥시뉴클레오사이드이고, 여기서 뉴클레오사이드 2 내지 3 및 17 내지 18 사이 인터뉴클레오사이드 연결기는 포스포디에스테르 인터뉴클레오사이드 연결기이고 뉴클레오사이드 1 내지 2, 3 내지 4, 4 내지 5, 5 내지 6, 6 내지 7, 7 내지 8, 8 내지 9, 9 내지 10, 10 내지 11, 11 내지 12, 12 내지 13, 13 내지 14, 14 내지 15, 15 내지 16, 16 내지 17, 18 내지 19, 및 19 내지 20 사이 인터뉴클레오사이드 연결기는 포스포로티오에이트 인터뉴클레오사이드 연결기이고, 상기 각 시토신은 5-메틸 시토신이다.

[0460] 화합물 번호: 934556은 하기 화학 표기법으로 특성규명될 수 있다: mCes Geo mCes Aes mCes Tds Tds Ads Ads mCds Ads Ads Tds Ads Tds mCes Aeo Tes Aes Te; 여기서,

[0461] A = 아데닌 핵염기,

[0462] mC = 5-메틸 시토신 핵염기,

[0463] G = 구아닌 핵염기,

[0464] T = 티민 핵염기

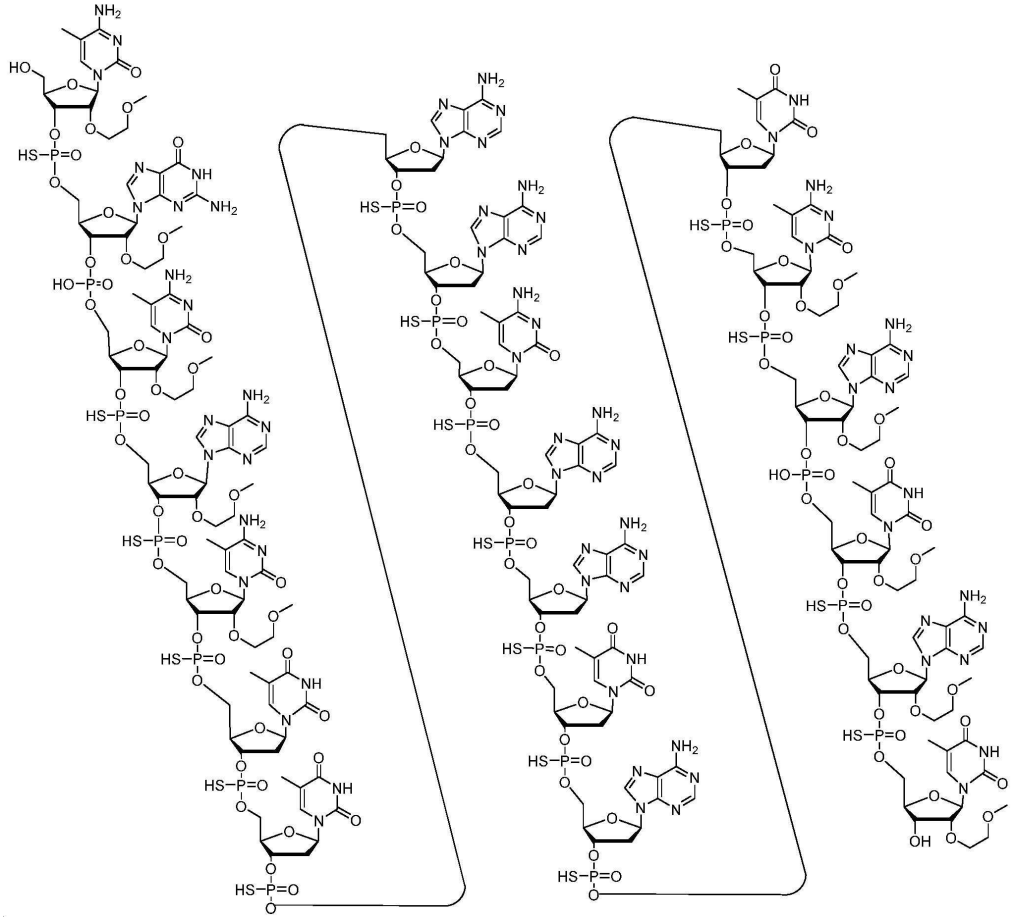
[0465] e = 2'-MOE 변형된 당,

[0466] d = 2'-데옥시리보오스 당,

[0467] s = 포스포로티오에이트 인터뉴클레오사이드 연결기, 및

[0468] o = 포스포디에스테르 인터뉴클레오사이드 연결기.

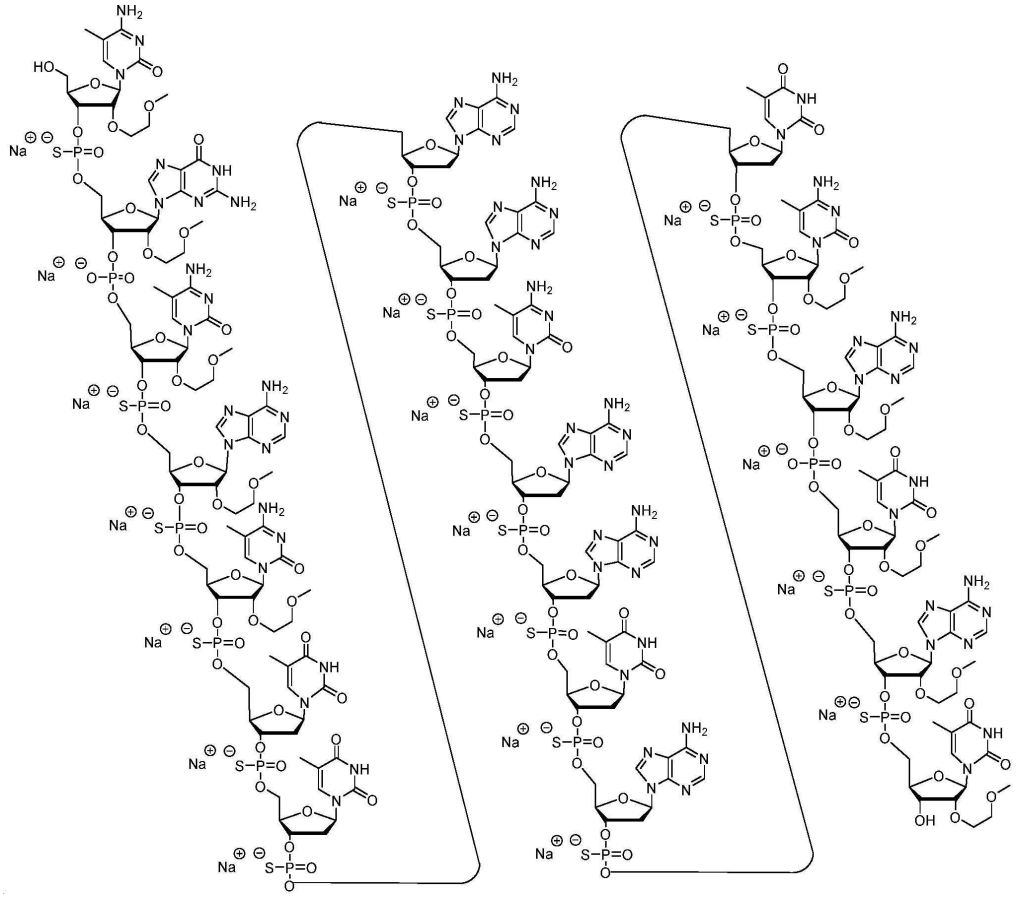
[0469] 화합물 번호: 934556은 하기 화학 구조로 나타낼 수 있다:



[0470]

[0471] **구조 11. 화합물 번호: 934556** (서열번호: 852).

[0472] 화합물 번호: 934556은 하기 화학 구조로 나타낼 수 있다:



[0473]

[0474] **구조 12. 화합물 번호: 934556의 나트륨 염** (서열번호: 852).

[0475] **VIII. 특정 핫스팟 영역**

[0476] 1. 서열번호: 2의 핵염기 18,633-18,658

[0477] 특정 구현예에서, 서열번호: 2의 핵염기 18,633-18,658은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 18,633-18,658에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 18,633-18,658에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0478] 서열번호: 852, 1997, 2073, 2148, 3513, 및 3590의 핵염기 서열은 서열번호: 2의 핵염기 18,633-18,658에 상보성이다.

[0479] 특정 구현예에서, 서열번호: 2의 핵염기 18,633-18,658에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 54% 감소를 달성한다.

[0480] 2. 서열번호: 2의 핵염기 21,721-21,755

[0481] 특정 구현예에서, 서열번호: 2의 핵염기 21,721-21,755는 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 21,721-21,755에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 21,721-21,755에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르

("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0482] 서열번호: 291, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 및 880의 핵염기 서열은 서열번호: 2의 핵염기 21,721-21,755에 상보성이다.

[0483] 특정 구현예에서, 서열번호: 2의 핵염기 21,721-21,755에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 52% 감소를 달성한다.

[0484] 3. 서열번호: 2의 핵염기 27,963-28,016

[0485] 특정 구현예에서, 서열번호: 2의 핵염기 27,963-28,016은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 27,963-28,016에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 27,963-28,016에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0486] 서열번호: 293, 886, 887, 888, 889, 890, 891, 892, 893, 및 3745의 핵염기 서열은 서열번호: 2의 핵염기 27,963-28,016에 상보성이다.

[0487] 특정 구현예에서, 서열번호: 2의 핵염기 27,963-28,016에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 39% 감소를 달성한다.

[0488] 4. 서열번호: 2의 핵염기 35,415-35,446

[0489] 특정 구현예에서, 서열번호: 2의 핵염기 35,415-35,446은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 35,415-35,446에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 35,415-35,446에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0490] 서열번호: 920, 921, 2378, 2454, 2530, 2606, 2683, 2759, 2835, 3061, 3137, 3212, 및 3288의 핵염기 서열은 서열번호: 2의 핵염기 35,415-35,446에 상보성이다.

[0491] 특정 구현예에서, 서열번호: 2의 핵염기 35,415-35,446에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 42% 감소를 달성한다.

[0492] 5. 서열번호: 2의 핵염기 77,221-77,264

[0493] 특정 구현예에서, 서열번호: 2의 핵염기 77,221-77,264는 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 77,221-77,264에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 77,221-77,264에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0494] 서열번호: 131, 217, 1106, 1107, 및 1108의 핵염기 서열은 서열번호: 2의 핵염기 77,221-77,264에 상보성이다.

[0495] 특정 구현예에서, 서열번호: 2의 핵염기 77,221-77,264에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 51% 감소를 달성한다.

[0496] 6. 서열번호: 2의 핵염기 81,581-81,612 및 87,838-87,869

[0497] 특정 구현예에서, 서열번호: 2의 핵염기 81,581-81,612 및 87,838-87,869는 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 81,581-81,612 및 87,838-87,869에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 81,581-81,612 및 87,838-87,869에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooossssssssssssooss.

[0498] 서열번호: 667, 668, 669, 670, 671, 1785, 1786, 1787, 1788, 1789, 1790, 1791, 및 1792의 핵염기 서열은 서열번호: 2의 핵염기 81,581-81,612 및 87,838-87,869에 상보성이다.

[0499] 특정 구현예에서, 서열번호: 2의 핵염기 81,581-81,612 및 87,838-87,869에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 38% 감소를 달성한다.

[0500] 7. 서열번호: 2의 핵염기 81,627-81,651

[0501] 특정 구현예에서, 서열번호: 2의 핵염기 81,627-81,651은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 81,627-81,651에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 81,627-81,651에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooossssssssssssooss.

[0502] 서열번호: 674, 1799, 1800, 1801, 1802, 및 1803의 핵염기 서열은 서열번호: 2의 핵염기 81,627-81,651에 상보성이다.

[0503] 특정 구현예에서, 서열번호: 2의 핵염기 81,627-81,651에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 66% 감소를 달성한다.

[0504] 8. 서열번호: 2의 핵염기 82,058-82,081

[0505] 특정 구현예에서, 서열번호: 2의 핵염기 82,058-82,081은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 82,058-82,081에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 82,058-82,081에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooossssssssssssooss.

[0506] 서열번호: 222, 1130, 1131, 1132, 및 1133의 핵염기 서열은 서열번호: 2의 핵염기 82,058-82,081에 상보성이다.

[0507] 특정 구현예에서, 서열번호: 2의 핵염기 82,058-82,081에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 53% 감소를 달성한다.

[0508] 9. 서열번호: 2의 핵염기 82,180-82,220

[0509] 특정 구현예에서, 서열번호: 2의 핵염기 82,180-82,220은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 82,180-82,220에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 82,180-82,220에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테

르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0510] 서열번호: 225, 1145, 2005, 2840, 3369, 3446, 3521, 3598, 및 3674의 핵염기 서열은 서열번호: 2의 핵염기 82,180-82,220에 상보성이다.

[0511] 특정 구현예에서, 서열번호: 2의 핵염기 82,180-82,220에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 64% 감소를 달성한다.

[0512] 10. 서열번호: 2의 핵염기 82,500-82,525

[0513] 특정 구현예에서, 서열번호: 2의 핵염기 82,500-82,525는 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 82,500-82,525에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 82,500-82,525에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0514] 서열번호: 439, 1807, 1808, 1809, 1810, 1811, 및 1812의 핵염기 서열은 서열번호: 2의 핵염기 82,500-82,525에 상보성이다.

[0515] 특정 구현예에서, 서열번호: 2의 핵염기 82,500-82,525에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 49% 감소를 달성한다.

[0516] 11. 서열번호: 2의 핵염기 91,038-91,067

[0517] 특정 구현예에서, 서열번호: 2의 핵염기 91,038-91,067은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 91,038-91,067에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 91,038-91,067에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0518] 서열번호: 692, 1826, 1827, 1828, 1829, 1830, 1831, 1832, 1833, 1834, 및 1835의 핵염기 서열은 서열번호: 2의 핵염기 91,038-91,067에 상보성이다.

[0519] 화합물 번호: 780642, 803664, 803665, 803666, 803667, 803668, 803669, 803670, 803671, 803672, 및 803673의 변형된 올리고뉴클레오타이드는 서열번호: 2의 뉴클레오타이드 91,038-91,067에 대해 상보적이다.

[0520] 특정 구현예에서, 서열번호: 2의 핵염기 91,038-91,067에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 42% 감소를 달성한다.

[0521] 12. 서열번호: 2의 핵염기 92,148-92,173

[0522] 특정 구현예에서, 서열번호: 2의 핵염기 92,148-92,173은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 92,148-92,173에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 92,148-92,173에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0523] 서열번호: 1213, 2613, 2690, 3143, 3219, 및 3295의 핵염기 서열은 서열번호: 2의 핵염기 92,148-92,173에 상

보성이다.

[0524] 특정 구현예에서, 서열번호: 2의 핵염기 92,148-92,173에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 59% 감소를 달성한다.

[0525] 13. 서열번호: 2의 핵염기 98,186-98,220

[0526] 특정 구현예에서, 서열번호: 2의 핵염기 98,186-98,220은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 98,186-98,220에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 98,186-98,220에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0527] 서열번호: 1231, 1232, 2462, 2538, 2614, 2691, 2767, 3069, 3144, 3220, 3296의 핵염기 서열은 서열번호: 2의 핵염기 98,186-98,220에 상보성이다.

[0528] 특정 구현예에서, 서열번호: 2의 핵염기 98,186-98,220에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 55% 감소를 달성한다.

[0529] 14. 서열번호: 2의 핵염기 98,218-98,242

[0530] 특정 구현예에서, 서열번호: 2의 핵염기 98,218-98,242는 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 98,218-98,242에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 98,218-98,242에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0531] 서열번호: 150, 1233, 2008, 3372, 3449, 및 3524의 핵염기 서열은 서열번호: 2의 핵염기 98,218-98,242에 상보성이다.

[0532] 특정 구현예에서, 서열번호: 2의 핵염기 98,218-98,242에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 38% 감소를 달성한다.

[0533] 15. 서열번호: 2의 핵염기 99,199-99,223

[0534] 특정 구현예에서, 서열번호: 2의 핵염기 99,199-99,223은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 2의 핵염기 99,199-99,223에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 99,199-99,223에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0535] 서열번호: 1243, 2311, 2387, 2920, 2995, 및 3755의 핵염기 서열은 서열번호: 2의 핵염기 99,199-99,223에 상보성이다.

[0536] 특정 구현예에서, 서열번호: 2의 핵염기 99,199-99,223에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 52% 감소를 달성한다.

[0537] 16. 서열번호: 2의 핵염기 119,903-119,936

[0538] 특정 구현예에서, 서열번호: 2의 핵염기 119,903-119,936은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs

는 서열번호: 2의 핵염기 119,903-119,936에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 2의 핵염기 119,903-119,936에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0539] 서열번호: 750, 1927, 1928, 1929, 1930, 1931, 1932, 1933, 1934, 1935, 2822, 2898, 3351, 및 3733의 핵염기 서열은 서열번호: 2의 핵염기 119,903-119,936에 상보성이다.

[0540] 특정 구현예에서, 서열번호: 2의 핵염기 119,903-119,936에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 51% 감소를 달성한다.

[0541] 17. 서열번호: 1의 핵염기 4,062-4,086

[0542] 특정 구현예에서, 서열번호: 1의 핵염기 4,062-4,086은 핫스팟 영역을 포함한다. 특정 구현예에서, siRNAs는 서열번호: 1의 핵염기 4,062-4,086에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 서열번호: 1의 핵염기 4,062-4,086에 상보성이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20개의 핵염기 길이이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머이다. 특정 구현예에서, 변형된 올리고뉴클레오타이드의 인터뉴클레오사이드 연결기는 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기이다. 특정 구현예에서, 포스포디에스테르 ("o") 및 포스포로티오에이트 ("s") 인터뉴클레오사이드 연결기는 5'부터 3'까지의 순서로 배열된다: sooosssssssssssooss.

[0543] 서열번호: 39, 231, 232, 233, 1161, 및 1162의 핵염기 서열은 서열번호: 1의 핵염기 4,062-4,086에 상보성이다.

[0544] 특정 구현예에서, 서열번호: 1의 핵염기 4,062-4,086에 상보성인 변형된 올리고뉴클레오타이드는 적어도 하나의 단일 용량 검정에서 *시험관내* LRRK2 RNA의 적어도 56% 감소를 달성한다.

[0545] 비제한 개시내용 및 참고에 의한 편입

[0546] 본 명세서에 열거된 각각의 문헌 및 특허 공보는 전체적으로 참고로 편입된다.

[0547] 본 명세서에 기재된 특정 화합물, 조성물 및 방법이 특정 구현예에 따라 특이성으로 기재되어 오면서, 하기 실시예는 본 명세서에 기재된 화합물을 단지 설명하도록 작용하고 동일한 것을 제한하기 위한 것은 아니다. 본원에서 인용된 각각의 참고문헌, 유전자은행 기탁 번호, 및 기타 등등은 그 전체가 참고로 본 명세서에 편입된다.

[0548] 본 출원에 첨부하는 서열 목록이 요구되는 바와 같이 어느 한쪽 "RNA" 또는 "DNA"로서 각 서열을 확인하여도, 실제로는, 그들 서열은 화학적 변형의 임의의 조합으로 변형될 수 있다. 당해 분야의 숙련가는 "RNA" 또는 "DNA"로서 그와 같은 지정이 임의의 특정 사례에서 변형된 올리고뉴클레오타이드를 기재한다는 것을 쉽게 인정할 것이다. 예를 들어, 2'-OH 당 모이어티 및 티민 염기를 포함하는 뉴클레오사이드를 포함하는 올리고뉴클레오타이드는 변형된 당 (DNA의 1개의 2'-H 대신 2'-OH)를 가지고 있는 DNA로서, 또는 변형된 염기 (RNA의 우라실 대신 티민 (메틸화된 우라실))을 가지고 있는 RNA로서 기재될 수 있다. 따라서, 비제한적으로 서열 목록에서의 것들을 포함하는, 본 명세서에 제공된 핵산 서열은, 비제한적으로 변형된 핵염기를 가지고 있는 그와 같은 핵산을 포함하는, 천연 또는 변형된 RNA 및/또는 DNA의 임의의 조합을 함유하는 핵산을 포괄하기 위한 것이다. 추가 예로서 및 제한 없이, 핵염기 서열 "ATCGATCG"를 가지고 있는 올리고머성 화합물은, 변형되든 또는 미변형되든, 비제한적으로, RNA 염기를 포함하는 그와 같은 화합물, 예컨대 서열 "AUCGAUCG"를 가지고 있는 것 및 일부 DNA 염기 및 일부 RNA 염기 예컨대 "AUCGATCG"를 가지고 있는 것을 포함하는, 그와 같은 핵염기 서열을 가지고 있는 임의의 올리고머성 화합물 그리고 다른 변형된 핵염기, 예컨대 "AT^{m}CGAUCG" (여기서 ^{m}C는 5-위치에서 메틸 기를 포함하는 시토신 염기를 나타낸다)를 가지고 있는 올리고머성 화합물을 포괄한다.

[0549] 본 명세서에 기재된 특정 화합물 (예를 들면, 변형된 올리고뉴클레오타이드)는 하나 이상의 비대칭 중심을 갖고 따라서, 절대적 입체화학 관점에서, (*R*) 또는 (*S*)로서, 예컨대 당 아노머에 대하여 α 또는 β로서, 또는 예컨대 아미노산에 대하여 (D) 또는 (L)로서, 정의될 수 있는 거울상이성질체, 부분입체이성질체, 및 다른 입체이성질체 배치형태, 등을 야기시킨다. 특정 입체이성질체 배치형태로 그려지는 또는 상기를 갖는 것으로서 기재되는

본 명세서에 제공된 화합물은 지시된 화합물만을 포함한다. 미정의된 입체화학으로 그려지는 또는 기재되는 본 명세서에 제공된 화합물은, 달리 특정되지 않는 한, 그것의 스테레오랜덤 및 광학적으로 순수한 형태를 포함하여, 모든 그와 같은 가능한 이성질체를 포함한다. 마찬가지로, 본 명세서에서 화합물의 호변이성질체 형태는 달리 나타내지 않는 한 또한 포함된다. 달리 나타내지 않는 한, 본 명세서에 기재된 화합물은 상응하는 염 형태를 포함하기 위한 것이다.

[0550] 본 명세서에 기재된 화합물은 하나 이상의 원자가 지시된 원소의 비-방사성 동위원소 또는 방사성 동위원소로 대체되는 변동을 포함한다. 예를 들어, 수소 원자를 포함하는 본 명세서에서의 화합물은 각각의 ^{1}H 수소 원자에 대하여 모든 가능한 중수소 치환을 포괄한다. 본 명세서에서의 화합물에 의해 포괄된 동위원소 치환은 하기를 비제한적으로 포함한다: ^{1}H 대신에 ^{2}H 또는 ^{3}H, ^{12}C 대신에 ^{13}C 또는 ^{14}C, ^{14}N 대신에 ^{15}N, ^{16}O 대신에 ^{17}O 또는 ^{18}O, 및 ^{32}S 대신에 ^{33}S, ^{34}S, ^{35}S, 또는 ^{36}S. 특정 구현예에서, 비-방사성 동위원소 치환은 치료 또는 연구 도구로서 사용에 유익한 올리고머성 화합물에 신규한 특성을 부여할 수 있다. 특정 구현예에서, 방사성 동위원소 치환은 연구 또는 진단 목적 예컨대 이미지형성에 적당한 화합물을 만들 수 있다.

[0551] **실시예**

[0552] 하기 실시예는 본 개시내용의 특정 구현예를 설명하고 비제한적이다. 더욱이, 특정 구현예가 제공되는 경우, 본 발명가는 그들 특정 구현예의 포괄적 적용을 고려하였다. 예를 들어, 특정 모티프를 가지고 있는 올리고뉴클레오타이드의 개시내용은 동일 또는 유사 모티프를 가지고 있는 추가의 올리고뉴클레오타이드를 지원한다. 그리고, 예를 들어, 특정 고-친화도 변형이 특정 위치에서 나타나는 경우, 동일 위치에서 다른 고-친화도 변형은, 달리 나타내지 않는 한, 적당히 고려된다.

[0553] **실시예 1: 인간 LRRK2 RNA 발현 *시험관내*, 단일 용량에서 포스포로티오에이트 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머의 효과**

[0554] 인간 LRRK2 핵산에 상보성인 변형된 올리고뉴클레오타이드는 *시험관내* LRRK2 RNA에서 그것의 효과에 대하여 설계 및 시험되었다.

[0555] 20,000 세포/웰의 밀도에서 배양된 SH-SY5Y 세포는 미처리된 대조군에 대하여 5,000 nM 농도의 변형된 올리고뉴클레오타이드로 또는 변형된 올리고뉴클레오타이드 없이 전기천공을 사용하여 형질감염되었다. 대략 24 시간 후, RNA는 세포로부터 단리되었고 LRRK2 RNA 수준은 정량적 실시간 PCR에 의해 측정되었다. 인간 프라이머 프로브 세트 RTS3133_MGB (정방향 서열 TTCCACACTTGCGGTCTTTAGA, 서열번호: 11로서 본 명세서에 지정됨; 역방향 서열 GCGGGACCTGGTAGGTACTG, 서열번호: 12로서 본 명세서에 지정됨; 프로브 서열 ATGAGCAGCAATGAT, 서열번호: 13으로서 본 명세서에 지정됨)은 RNA 수준을 측정하는데 사용되었다. LRRK2 RNA 수준은, RIBOGREEN®에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다. 결과는 미처리된 대조군 세포에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다. 별표 (*)로 표시된 퍼센트 대조군 값을 가진 변형된 올리고뉴클레오타이드는 프라이머 프로브 세트의 앰플리콘 영역을 표적화한다. 추가의 검정은 앰플리콘 영역을 표적화하는 올리고뉴클레오타이드의 효력 및 효능을 측정하는데 사용될 수 있다.

[0556] 표 1에서 변형된 올리고뉴클레오타이드는 5-10-5 MOE 갭머이다. 갭머는 20개의 핵염기 길이이고, 여기서 중심 갭 단편은 10개의 2'-데옥시뉴클레오사이드를 포함하고, 5개의 2'-MOE 뉴클레오사이드를 포함하는 5' 말단 및 3' 말단 둘 모두에서 윙 단편에 의해 측접된다. 갭머용 당 모티프는 (5'부터 3'까지) 하기이고: eeeeeddddddddddeeeee; 여기서 'd'는 2'-데옥시리보오스 당을 나타내고 'e'는 2'-MOE 변형된 당을 나타낸다. 각 인터뉴클레오사이드 연결기는 포스포로티오에이트 인터뉴클레오사이드 연결기이고 각 시토신 잔기는 5-메틸시토신이다. "개시 부위"는 갭머가 인간 핵산 서열에서 상보성인 5'-최말단 뉴클레오사이드를 나타낸다. "중단 부위"는 갭머가 인간 핵산 서열에서 상보성인 3'-최말단 뉴클레오사이드를 나타낸다.

[0557] 표 1에서 열거된 각 변형된 올리고뉴클레오타이드는, 명시된 바와 같이, 인간 LRRK2 핵산 서열 서열번호: 1 또는 서열번호: 2에 상보성이다. 'N/A'는 변형된 올리고뉴클레오타이드가 100% 상보성을 가진 그 특정 핵산에 상보성이지 않다는 것을 나타낸다. 아래 나타난 바와 같이, 인간 LRRK2 RNA의 서열에 상보성인 변형된 올리고뉴클레오타이드는 인간 LRRK2 RNA의 양을 감소시켰다.

표 1

포스포로티오에이트 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열	LRRK2 % 대조군	서열 번호
422420	368	387	10392	10411	ATTAATTTGCACAGAAGTGA	75	30
422421	375	394	10399	10418	GACTTCTATTAATTTGCACA	65	31
422425	441	460	10465	10484	ACCAAGGACTTCCCAATCAT	111	32
422428	606	625	16126	16145	GTGCATGGCATCAAAAATTA	35	33
422433	1791	1810	52705	52724	TCCACATTTCTGAATCCCAG	24	34
422435	1904	1923	N/A	N/A	TCTTGGTCATCTGGATACAT	76	35
422436	1913	1932	N/A	N/A	CACTGAATTTCTTGGTCATC	84	36
422437	1919	1938	N/A	N/A	CCCAGACACTGAATTTCTTG	53	37
422450	3886	3905	N/A	N/A	GAGGAATCTCTTTCAGTTTA	58	38
422451	4064	4083	84059	84078	AACCTTATGATGTCTTTGGC	44	39
422456	4472	4491	88573	88592	GAAACATCCAAATGTGTGCC	64	40
422457	4484	4503	88585	88604	TGCTTCTCATCAGAAACATC	66	41
422458	4580	4599	88681	88700	TCCTCGGTGGCATTCACAAA	96	42
422461	4908	4927	93369	93388	CCACTTGGGTTCCACAAAGT	39	43
422462	4915	4934	93376	93395	TACAAAGCCACTTGGGTTCC	57	44
422466	5480	5499	100469	100488	GGAAACCATTCTTCCATGAG	85	45
422469	5702	5721	101340	101359	TTTCTAGGCAGGTCAGCCAA	74	46
422470	5978	5997	113175	113194	AGCAGGCGATCCAAGGAACC	90	47
422472	6139	6158	118472	118491	CAATGATGGCAGCATTGGGA	72	48
422475	6260	6279	124891	124910	TGTTGGTTATAAATGACATT	81	49
422477	6461	6480	126577	126596	TGAGGATTTTCTTTCAAACA	96	50
422479	6500	6519	129645	129664	TTCAAAATGTCAAAGACCTG	98	51
422480	6841	6860	132551	132570	AAGTGACAGAATCAGTCATC	83	52
422483	7108	7127	137512	137531	TGAGTTTCTGAATGGTGAAA	92	53
438386	117	136	3236	3255	GCTGCCACTAGCCATGGTGG	99	54
438387	185	204	3304	3323	TCCTGGACATTGTTCAGCCT	48	55
438388	381	400	10405	10424	TGGACAGACTTCTATTAATT	73	56
438401	3944	3963	83939	83958	AGTTCCAAGTTGTAACTGAC	71	57
438405	4408	4427	87312	87331	AGAGCCAAGGCTTCATGGCA	98	58
438408	4619	4638	88720	88739	TTTATGATGGTTTTCCGAAG	107	59
438410	4649	4668	N/A	N/A	TGATCTCGGATCTTGAAATT	88	60
438429	8882	8901	147051	147070	ATGAATACTGGTCAGGGCCA	77	61
438432	N/A	N/A	4483	4502	AAACTGATTTCAGTTCCCCA	50	62
438433	N/A	N/A	52819	52838	ACCTTGGTCATCTGGATACA	93	63
438434	N/A	N/A	92072	92091	TGATCTCGGATCTATGAAAT	94	64
438436	N/A	N/A	114858	114877	CCCCTGGTGTTCAAAAGCAG	69	65
438437	N/A	N/A	129638	129657	TGTCAAAGACCTGAGAAAGT	116	66
438538	171	190	3290	3309	CAGCCTGACTATCAACTTCT	35	67

[0558]

[0559]

438539	436	455	10460	10479	GGACTTCCCAATCATTTCCA	90	68
438540	1074	1093	N/A	N/A	GAAAATAGTCTCAGTGAGGA	70	69
438541	1078	1097	N/A	N/A	TTAAGAAAATAGTCTCAGTG	98	70
438542	2275	2294	56283	56302	CCATGATGCTGTTATTCTGA	54	71
438543	2282	2301	56290	56309	CATTCAACCATGATGCTGTT	50	72
438544	2361	2380	61982	62001	GCTCTCTTTCTCACATACCT	22	73
438545	2366	2385	61987	62006	GGACTGCTCTCTTTCTCACA	26	74
438546	2525	2544	62146	62165	AATCCTCCAAGGCAAATGCT	55	75
438547	2564	2583	62185	62204	AAAGGACCAAGCCAAGAAGG	58	76
438548	2571	2590	62192	62211	TGGAAATAAAGGACCAAGCC	27	77
438549	2759	2778	65597	65616	ACACTGTCCATAGAAGAGTC	56	78
438550	2764	2783	65602	65621	CAAACACACTGTCCATAGAA	44	79
438551	3503	3522	77252	77271	AAAATCTTCAGTTCCTTCAG	82	80
438552	3857	3876	82202	82221	AGATGCAGTTTCTCTACTCT	67	81
438553	4300	4319	N/A	N/A	CCTCACGACCTGCAAAATCC	65	82
438554	4305	4324	N/A	N/A	GAATTCCTCACGACCTGCAA	77	83
438555	4480	4499	88581	88600	TCTCATCAGAAACATCCAAA	77	84
438556	4575	4594	88676	88695	GGTGGCATTCACAAAGTGGT	52	85
438557	4641	4660	N/A	N/A	GATCTTGAAATTAAGGCTCT	69	86
438558	5225	5244	99231	99250	AATCTTGACCAAAATCCCAT	79	87
438559	5530	5549	100519	100538	TCTTCAACAGAGTTTCTCCT	81	88
438560	5537	5556	100526	100545	GCCCATTTCTTCAACAGAGT	30	89
438561	5568	5587	100557	100576	ATGTTCTTCACCATCATTAA	98	90
438562	5735	5754	101373	101392	TCAAATTCCAACTCATCATT	111	91
438563	5825	5844	106516	106535	AAAATCTTCACAGCCACTTC	109	92
438564	5829	5848	106520	106539	ATTAAAAATCTTCACAGCCA	136	93
438565	6000	6019	113197	113216	GAGGCTGGCTTTGTCCTGCT	52	94
438566	6074	6093	118407	118426	ATAATCATGGCTGAGTGGAG	83	95
438567	6135	6154	118468	118487	GATGGCAGCATTGGGATACA	90	96
438568	6401	6420	126517	126536	CCATATTCTTTAACTGGATC	74	97
438569	6427	6446	126543	126562	TCTCAACCATAGGCCATGGG	47	98
438570	6465	6484	126581	126600	TTCTTGAGGATTTTCTTTCA	106	99
438571	6494	6513	N/A	N/A	ATGTCAAAGACCTGGGCAGA	107	100
438572	6572	6591	129717	129736	GCAACCATGCATTCAACAAT	76	101
438573	6696	6715	132406	132425	TCTACTATCAGCAACTTCCT	89	102
438574	6845	6864	132555	132574	AAACAAGTGACAGAATCAGT	110	103
438575	7632	7651	145801	145820	GTGTTTTTCTAAATTTTGCA	65	104
438576	7640	7659	145809	145828	ACTTCAATGTGTTTTTCTAA	105	105
438577	N/A	N/A	3658	3677	AAATAACTTGGAGGCTGGAA	114	106
438578	N/A	N/A	4487	4506	GACAAAACTGATTTCAGTTC	82	107
438579	N/A	N/A	77354	77373	CACTTACCAAGAAAATTCAT	118	108
438580	N/A	N/A	116733	116752	ATTATAGAATTTAATCTTAA	96	109
438581	N/A	N/A	142937	142956	ACCTCCCTAGAACCATAAAG	104	110
438582	60	79	3179	3198	TCCGCTGCTCAGGGAACCGG	65	111
438583	449	468	10473	10492	TGGTGAACACCAAGGACTTC	55	112
438584	457	476	N/A	N/A	GAATCAATTGGTGAACACCA	63	113
438585	529	548	13795	13814	GGAGGAGATCTAAGGTCTTC	90	114
438586	550	569	N/A	N/A	AGGTGATTTTACCTGAAGTT	64	115

438587	624	643	16144	16163	ATCATTGGCTGGAAATGAGT	51	116
438588	883	902	21714	21733	GGAATGCTTTCATAGCTTCC	56	117
438589	1166	1185	29427	29446	TTGTAACAGGCTTCCAGCCA	53	118
438590	1300	1319	N/A	N/A	CCCTATGAGCTGGGAAATGG	79	119
438591	1534	1553	N/A	N/A	CCAGGGAAGTGTTGCTTCCT	77	120
438592	1610	1629	37659	37678	TCCAGCTGCACTGGTAATGA	90	121
438593	1774	1793	N/A	N/A	CAGGATTTCCAATGAACCTG	72	122
438594	1885	1904	52799	52818	TCTGCAGTGTGTGAAGCACT	76	123
438595	2108	2127	56042	56061	TGATGCACCAGCAGCTTAGA	48	124
438596	2318	2337	56326	56345	TTTGCTTGATTGGCATCTGC	55	125
438597	2380	2399	62001	62020	GTTCCACCAATTTGGGACTG	34	126
438598	2412	2431	62033	62052	ATCTTGTTCACGAGATCCAC	70	127
438599	2515	2534	62136	62155	GGCAAATGCTATTGTTGGCC	63	128
438600	3171	3190	73707	73726	GAGTGCATTCTGGTGAAGCT	70	129
438601	3211	3230	N/A	N/A	AACTCTTCAGAGTTTCACAT	94	130
438602	3475	3494	77224	77243	GGGAGCATATCCCTGATATT	42	131
438603	3565	3584	77314	77333	CTTTAGGACAAGCCTCAAGA	71	132
438604	3702	3721	N/A	N/A	AGACCGCAAGTGTGGAAGAT	17*	133
438605	3707	3726	N/A	N/A	TCTAAAGACCGCAAGTGTGG	22*	134
438606	3930	3949	83925	83944	ACTGACATCCAGAGATGTCA	126	135
438607	3952	3971	83947	83966	AGGATCTTAGTTCCAAGTTG	95	136
438608	3957	3976	83952	83971	GGGAAAGGATCTTAGTTCCA	70	137
438609	3969	3988	83964	83983	CCCCATTTCATTGGGAAAGG	77	138
438610	4190	4209	86685	86704	CCAAGATCTGATTTCTTGGT	104	139
438611	4353	4372	87257	87276	AGCAAGGTACAATGCTCGCT	69	140
438612	4395	4414	87299	87318	CATGGCATCAACTTCAGCCT	83	141
438613	4413	4432	87317	87336	ATTGAAGAGCCAAGGCTTCA	94	142
438614	4422	4441	N/A	N/A	AGCCTTTATATTGAAGAGCC	103	143
438615	4428	4447	N/A	N/A	AGCGCGAGCCTTTATATTGA	91	144
438616	4433	4452	N/A	N/A	GAAGAAGCGCGAGCCTTTAT	66	145
438617	4544	4563	88645	88664	GCAGGGAACCCTCGCTTATT	97	146
438618	4682	4701	92105	92124	TAGCAGTCTGGAATCAGCTG	89	147
438619	4816	4835	92239	92258	CGTGAGGAAGCTCATTTTCA	70	148
438620	4963	4982	98111	98130	GTTTTGGACAACCTTCCACT	96	149
438621	5074	5093	98222	98241	TCTGGAATTTTTCTAGGAGC	62	150
438622	5116	5135	98264	98283	TGCTTGGAACCAGCAAATAT	78	151
438623	5451	5470	100440	100459	GTGGTCCACAACTTGGCCCA	71	152
438624	5745	5764	101383	101402	TGGAGCTTGTTCAAATTCCA	104	153
438625	5887	5906	113084	113103	GGTGGAGGTGGCAAAGCACC	78	154
438626	5968	5987	113165	113184	CCAAGGAACCCTTGGAGGCT	97	155
438627	5986	6005	113183	113202	CCTGCTGAAGCAGGCGATCC	75	156
438628	5991	6010	113188	113207	TTTGTCCTGCTGAAGCAGGC	89	157
438629	6058	6077	N/A	N/A	GGAGGTATCTCAAACCATCA	111	158
438630	6149	6168	118482	118501	GCAATCTTTGCAATGATGGC	72	159
438631	6157	6176	118490	118509	CGTAGTCAGCAATCTTTGCA	78	160
438632	6581	6600	129726	129745	TGATGTGTAGCAACCATGCA	62	161
438633	6586	6605	129731	129750	TGTTGTGATGTGTAGCAACC	77	162
438634	6613	6632	129758	129777	AGCCCAGCCAAATGCTTGCA	97	163

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438635	6624	6643	129769	129788	GGTGTGCCCACAGCCCAGCC	70	164
438636	6677	6696	129822	129841	TCAGAAGTGTATCCTTCAGT	95	165
438637	7373	7392	143021	143040	GCAGTGTTCTTCTGAAGGCA	100	166
438638	7482	7501	143130	143149	TGTCATCATGACTCTGACCG	74	167
438639	8333	8352	146502	146521	AGGACTTTGACAGTATGTCA	66	168
438640	8696	8715	146865	146884	TCCTTCAGCAACTGAAAAGT	85	169
438641	8748	8767	146917	146936	TGGAAGCCTAGGGTGGCAGA	62	170
438642	8914	8933	147083	147102	AGTTGTCCTATCACAGGGAA	90	171
438643	N/A	N/A	78939	78958	ATCAGATTCCCCTGAGGTAC	93	172
438644	N/A	N/A	78947	78966	CAGTCTGAATCAGATTCCCC	85	173
438645	N/A	N/A	143365	143384	GTTCAGCTGCAGTAATCTGC	67	174
438646	N/A	N/A	143372	143391	ACTGAGTGTTCAGCTGCAGT	80	175
438647	N/A	N/A	143377	143396	CCCAAACTGAGTGTTCAGCT	99	176
438648	N/A	N/A	10479	10498	ACTTACTGGTGAACACCAAG	121	177
438649	N/A	N/A	31012	31031	ATGAGCTGGGAAACTTTCAA	84	178
438650	N/A	N/A	41888	41907	TCTGGCATGCCTAAATGCAC	101	179
438651	N/A	N/A	52827	52846	TTGTACTGACCTTGGTCATC	126	180
438652	N/A	N/A	76342	76361	TCTTCAGAGTCTGAAAAGAC	83	181
438653	N/A	N/A	88530	88549	AAGCGCGAGCCTGGAGGGAA	89	182
438654	N/A	N/A	118392	118411	TGGAGGTATCTGCCAGAAAA	91	183
438655	N/A	N/A	118553	118572	ATCACCTACCTGGTGTGCCC	122	184

[0561]

[0562] **실시예 2: 인간 LRRK2 RNA 발현 *시험관내*, 단일 용량에서 혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머의 효과**

[0563] 인간 LRRK2 핵산에 상보성인 변형된 올리고뉴클레오타이드는 *시험관내* LRRK2 RNA에서 그것의 효과에 대하여 설계 및 시험되었다. 변형된 올리고뉴클레오타이드는 유사한 배양 조건을 가졌던 일련의 실험에서 시험되었다.

[0564] 20,000 세포/웰의 밀도에서 배양된 SH-SY5Y 세포는 미처리된 대조군에 대하여 5,000 nM 농도의 변형된 올리고뉴클레오타이드로 또는 변형된 올리고뉴클레오타이드 없이 전기천공을 사용하여 형질감염되었다. 대략 24 시간 후, RNA는 세포로부터 단리되었고 LRRK2 RNA 수준은 정량적 실시간 PCR에 의해 측정되었다. 인간 프라이머 프로브 세트 RTS3132 (정방향 서열 CATCACTCAGGCTGTTAAGACAAGA, 서열번호: 14로서 본 명세서에 지정됨; 역방향 서열 CAGCTGCCAGCAAAGATATCAA, 서열번호: 15로서 본 명세서에 지정됨; 프로브 서열 CTTTGCCACCTCCACCACCCCA, 서열번호: 16으로서 본 명세서에 지정됨), RTS3133_MGB (정방향 서열 TTCCACACTTGCGGTCTTTAGA, 서열번호: 11로서 본 명세서에 지정됨; 역방향 서열 GCGGGACCTGGTAGGTACTG, 서열번호: 12로서 본 명세서에 지정됨; 프로브 서열 ATGAGCAGCAATGAT, 서열번호: 13으로서 본 명세서에 지정됨), 및 RTS3146_MGB (정방향 서열 GAGCTTCCTCACGCAGTTCAC, 서열번호: 17로서 본 명세서에 지정됨; 역방향 서열 TGCTGGGTCTTGAAAATGAAGA, 서열번호: 18로서 본 명세서에 지정됨; 프로브 서열 TTCTAAATGAATCAGGAGTCC, 서열번호: 19로서 본 명세서에 지정됨)은 RNA 수준을 측정하는데 사용되었다. LRRK2 RNA 수준은, RIBOGREEN®에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다. 결과는 미처리된 대조군 세포에 비하여 퍼센트 대조군 LRRK2 RNA 수준으로서 아래 표에서 제시된다. 별표 (*)로 표시된 퍼센트 대조군 값을 가진 변형된 올리고뉴클레오타이드는 프라이머 프로브 세트의 앰플리콘 영역을 표적화한다.

[0565] 표 2에서 변형된 올리고뉴클레오타이드는 5-10-5 MOE 갭머이다. 갭머는 20개의 핵염기 길이이고, 여기서 중심 갭 단편은 10개의 2'-데옥시뉴클레오사이드를 포함하고, 5개의 2'-MOE 뉴클레오사이드를 포함하는 5' 말단 및 3' 말단 둘 모두에서 윙 단편에 의해 측접된다. 갭머용 당 모티프는 (5'부터 3'까지) 하기이고: eeeeeddddddddddeeeee; 여기서 'd'는 2'-데옥시리보오스 당을 나타내고 'e'는 2-MOE 변형된 당을 나타낸다. 각 갭머 전반에 걸쳐 모든 시토신 잔기는 5-메틸 시토신이다. 각 갭머용 인터뉴클레오사이드 연결기는 혼합된 포스포디에스테르 및 포스포로티오에이트 연결기이다. 갭머용 인터뉴클레오사이드 연결기 모티프는 (5'부터 3'까지) 하기이고: sooosssssssssssooss; 여기서 'o'는 포스포디에스테르 인터뉴클레오사이드 연결기를 나타내고 's'는 포스포로티오에이트 인터뉴클레오사이드 연결기를 나타낸다. "개시 부위"는 갭머가 인간 핵산 서열에서 상보성인 5'-최말단 뉴클레오사이드를 나타낸다. "중단 부위"는 갭머가 인간 핵산 서열에서 상보성인 3'-최말단 뉴클레오사이드를 나타낸다.

[0566] 표 2에서 열거된 각 변형된 올리고뉴클레오타이드는, 명시된 바와 같이, 인간 LRRK2 핵산 서열 서열번호: 1 또는 서열번호: 2에 상보성이다. 'N/A'는 변형된 올리고뉴클레오타이드가 100% 상보성을 가진 그 특정 핵산 서열에 상보성이지 않다는 것을 나타낸다. 아래 나타난 바와 같이, 인간 LRRK2 RNA의 서열에 상보성인 변형된 올리고뉴클레오타이드는 인간 LRRK2 RNA의 양을 감소시켰다.

표 2

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군 RTS3132	LRRK2 % 대조군 RTS3133 _MGB	LRRK2 % 대조군 RTS3146 _MGB	서열 번호
693423	4064	4083	84059	84078	AACCTTATGATGTCTTTGGC	15	31	18	39
693424	4908	4927	93369	93388	CCACTTGGGTTCCACAAAGT	24	31	24	43
693428	2361	2380	61982	62001	GCTCTCTTTCTCACATACCT	10	14	11	73
693429	2571	2590	62192	62211	TGGAAATAAAGGACCAAGCC	26	31	27	77
780202	2368	2387	61989	62008	TGGGACTGCTCTCTTTCTCA	19	26	20	185
780203	2371	2390	61992	62011	ATTTGGGACTGCTCTCTTTC	28	36	32	186
780204	2406	2425	62027	62046	TTCACGAGATCCACTATTCA	48	51	51	187
780205	2451	2470	62072	62091	GTCACCTTTCCCAATGCTTA	21	35	29	188
780206	2499	2518	62120	62139	GGCCACATCCAGGGCCAGCC	56	62	45	189
780207	2543	2562	62164	62183	TCAACTTTTCCTATACAAAA	38	42	47	190
780208	2566	2585	62187	62206	ATAAAGGACCAAGCCAAGAA	53	56	64	191
780209	2569	2588	62190	62209	GAAATAAAGGACCAAGCCAA	48	53	54	192
780210	2573	2592	62194	62213	TCTGGAAATAAAGGACCAAG	21	24	27	193
780211	2576	2595	62197	62216	TTATCTGGAAATAAAGGACC	39	37	41	194
780212	2587	2606	62208	62227	AATTAGAAGTCTTATCTGGA	59	61	59	195
780213	2632	2651	65470	65489	TCACCATTCTTGCTAGTGTA	41	42	50	196
780214	2678	2697	65516	65535	CCTGAGGCTGTTCCTTCTTC	37	47	44	197
780215	2722	2741	65560	65579	CATCAAATTTAGACAGCACA	41	44	48	198
780216	2759	2778	65597	65616	ACACTGTCCATAGAAGAGTC	50	48	45	78
780217	2762	2781	65600	65619	AACACACTGTCCATAGAAGA	41	47	43	199
780218	2764	2783	65602	65621	CAAACACACTGTCCATAGAA	31	39	37	79
780219	2766	2785	65604	65623	AGCAAACACACTGTCCATAG	21	27	24	200
780220	2769	2788	65607	65626	TTGAGCAAACACACTGTCCA	34	37	36	201
780221	2810	2829	71653	71672	AGAAATGAGCCTTCACTTCC	35	49	41	202
780222	2854	2873	71697	71716	GGTAAAATTCTCCTACACTA	37	39	38	203
780223	2898	2917	71741	71760	ATGTCTTTGCAAATTTGGTG	41	46	38	204
780224	2942	2961	72966	72985	TTCAGTAAATCTTCATGATC	55	57	64	205
780225	2986	3005	N/A	N/A	ATGACCTGAGTGAATCATCT	51	46	55	206
780226	3031	3050	73567	73586	GAGAAGAAATGCTGTCTGAA	54	61	62	207
780227	3075	3094	73611	73630	TGCTGAAAGGTCTAGTGATG	34	37	37	208
780228	3120	3139	73656	73675	TATACAGCATTTCTGGCTTA	61	79	59	209
780229	3164	3183	73700	73719	TTCTGGTGAAGCTCCAGCTT	27	32	29	210
780230	3208	3227	N/A	N/A	TCTTCAGAGTTTCACATAGC	62	70	61	211
780231	3256	3275	76390	76409	AAGGAAATGATGTAAATTTA	65	70	69	212
780232	3300	3319	76434	76453	AGAGACATCAAGATTAGCAA	24	33	35	213
780233	3344	3363	76478	76497	TTCACTGTAGGATCTAAAAC	46	45	45	214
780234	3389	3408	76523	76542	GACAGCTGGTTATATGACAG	30	31	29	215
780235	3433	3452	76567	76586	GCTCCAGTTTCTCTACCACA	41	40	50	216

[0567]

780236	3494	3513	77243	77262	AGTTCCTTCAGTCTCAAGGG	16	31	22	217
780237	3538	3557	77287	77306	CTGATAGGGATGAAATGTGG	27	31	28	218
780238	3582	3601	77331	77350	GGCACTGAAACTCTCCACTT	25	37	27	219
780239	3626	3645	80906	80925	ATAGAAGGAGGCAAGAAAGG	47	60	67	220
780240	3670	3689	80950	80969	CTGGAATACAGGAAAATTTG	52	44	51	221
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	10	3*	13	222
780242	3758	3777	82103	82122	GATTTCCAGTGTGCGGGACC	27	20*	33	223
780243	3802	3821	82147	82166	TGCTGATCTGATTATGGCTA	22	36	33	224
780244	3846	3865	82191	82210	CTCTACTCTAGACCATAAAT	25	32	28	225
780245	3891	3910	N/A	N/A	CTCAGGAGGAATCTCTTTCA	43	47	51	226
780246	3935	3954	83930	83949	TTGTAACTGACATCCAGAGA	63	75	74	227
780247	3979	3998	83974	83993	TGCTTAATTTCCCCATTTCA	23	41	37	228
780248	4023	4042	84018	84037	ATCAAAGTTAAGATGCAGTT	25	30	29	229
780249	4059	4078	84054	84073	TATGATGTCTTTGGCTTTAC	33	41	36	230
780250	4062	4081	84057	84076	CCTTATGATGTCTTTGGCTT	28	34	31	231
780251	4066	4085	N/A	N/A	GAAACCTTATGATGTCTTTG	42	39	41	232
780252	4067	4086	N/A	N/A	AGAAACCTTATGATGTCTTT	34	45	50	233
780253	4069	4088	N/A	N/A	GAAGAAACCTTATGATGTCT	44	61	47	234
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	17	24	14	235
780255	4155	4174	86650	86669	CAATAAGGTGGTTTTACCAC	35	51	47	236
780256	4199	4218	86694	86713	CTTTGCATTCCAAGATCTGA	30	33	32	237
780257	4243	4262	86738	86757	TTATTTGGATAGGCCAGTCT	34	42	50	238
780258	4287	4306	86782	86801	AAAATCCCACACATTTAGGA	54	60	57	239
780259	4350	4369	87254	87273	AAGGTACAATGCTCGCTGCG	51	65	51	240
780260	4394	4413	87298	87317	ATGGCATCAACTTCAGCCTG	45	41	49	241
780261	4438	4457	88539	88558	GGGAAGAAGAAGCGCGAGCC	29	41	32	242
780262	4483	4502	88584	88603	GCTTCTCATCAGAAACATCC	30	41	35	243
780263	4527	4546	88628	88647	ATTCAGGAGTTCCTTGGTGA	43	85	47	244
780264	4571	4590	88672	88691	GCATTCACAAAGTGGTAATC	35	43	35	245
780265	4615	4634	88716	88735	TGATGGTTTTCCGAAGTTTT	43	46	49	246
780266	4659	4678	92082	92101	AACAACAAGCTGATCTCGGA	49	57	56	247
780267	4703	4722	92126	92145	ATGATTTTTTCAAGTTCTAC	31	47	45	248
780268	4747	4766	92170	92189	CAATTACGGGAAATTCAATT	68	60	57	249
780269	4791	4810	92214	92233	CTGCAGCTGATTTTCTCTCA	23	32	27	250
780270	4835	4854	92258	92277	TCATTTAGAAAGTGAACTGC	40	51	54*	251
780271	4883	4902	93344	93363	TCACTTAACTGCAGTGCTGG	27	38	10*	252
780272	4903	4922	93364	93383	TGGGTTCCACAAAGTACAAG	41	47	42	253
780273	4906	4925	93367	93386	ACTTGGGTTCCACAAAGTAC	42	38	38	254
780274	4910	4929	93371	93390	AGCCACTTGGGTTCCACAAA	28	43	30	255
780275	4913	4932	93374	93393	CAAAGCCACTTGGGTTCCAC	31	43	38	256

[0568]

[0569] **실시예 3: 인간 LRRK2 RNA 발현 *시험관내*, 단일 용량에서 혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머의 효과**

[0570] 인간 LRRK2 핵산에 상보성인 변형된 올리고뉴클레오타이드는 *시험관내* LRRK2 RNA에서 그것의 효과에 대하여 설계 및 시험되었다. 변형된 올리고뉴클레오타이드는 유사한 배양 조건을 가졌던 일련의 실험에서 시험되었다.

[0571] 20,000 세포/웰의 밀도에서 배양된 SH-SY5Y 세포는 미처리된 대조군에 대하여 3,000 nM 농도의 변형된 올리고뉴클레오타이드로 또는 변형된 올리고뉴클레오타이드 없이 전기천공을 사용하여 형질감염되었다. 대략 24 시간 후, RNA는 세포로부터 단리되었고 LRRK2 RNA 수준은 실시예 2에서 기재된 바와 같이 인간 프라이머 프로브 세트 RTS3132를 사용하여 정량적 실시간 PCR에 의해 측정되었다. LRRK2 RNA 수준은, RIBOGREEN®에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다. 결과는 미처리된 대조군 세포에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다. 별표 (*)로 표시된 퍼센트 대조군 값을 가진 변형된 올리고뉴클레오타이드는 프라이머 프로브 세트의 앰플리콘 영역을 표적화한다. 추가의 검정은 앰플리콘 영역을 표적화하는 올리고뉴클레오타이드의 효력 및 효능을 측정하는데 사용될 수 있다.

[0572] 표 3-9에서 변형된 올리고뉴클레오타이드는 5-10-5 MOE 갭머이다. 갭머는 20개의 핵염기 길이이고, 여기서 중심 갭 단편은 10개의 2'-데옥시뉴클레오사이드를 포함하고, 5개의 2'-MOE 뉴클레오사이드를 포함하는 5' 말단 및 3' 말단 둘 모두에서 윙 단편에 의해 측접된다. 갭머용 당 모티프는 (5'부터 3'까지) 하기이고: eeeeeddddddddddeeeee; 여기서 'd'는 2'-데옥시리보오스 당을 나타내고 'e'는 2-MOE 변형된 당을 나타낸다. 각 갭머 전반에 걸쳐 모든 시토신 잔기는 5-메틸 시토신이다. 각 갭머용 인터뉴클레오사이드 연결기는 혼합된 포스포디에스테르 및 포스포로티오에이트 연결기이다. 갭머용 인터뉴클레오사이드 연결기 모티프는 (5'부터 3'까지) 하기이고: soooosssssssssssooss; 여기서 'o'는 포스포디에스테르 인터뉴클레오사이드 연결기를 나타내고 's'는 포스포로티오에이트 인터뉴클레오사이드 연결기를 나타낸다. "개시 부위"는 갭머가 인간 핵산 서열에서 상보성인 5'-최말단 뉴클레오사이드를 나타낸다. "중단 부위"는 갭머가 인간 핵산 서열에서 상보성인 3'-최말단 뉴클

레오사이드를 나타낸다.

[0573] 표 3-9에서 열거된 각 변형된 올리고뉴클레오타이드는, 명시된 바와 같이, 인간 LRRK2 핵산 서열 서열번호: 1 또는 서열번호: 2에 상보성이다. 'N/A'는 변형된 올리고뉴클레오타이드가 100% 상보성을 가진 그 특정 핵산 서열에 상보성이지 않다는 것을 나타낸다. 아래 나타난 바와 같이, 인간 LRRK2 RNA의 서열에 상보성인 변형된 올리고뉴클레오타이드는 인간 LRRK2 RNA의 양을 감소시켰다.

표 3

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
690092	171	190	3290	3309	CAGCCTGACTATCAACTTCT	57	67
690093	2366	2385	61987	62006	GGACTGCTCTCTTTCTCACA	70	74
693420	606	625	16126	16145	GTGCATGGCATCAAAAATTA	41	33
693421	1791	1810	52705	52724	TCCACATTTCTGAATCCCAG	48	34
693428	2361	2380	61982	62001	GCTCTCTTTCTCACATACCT	51	73
693438	883	902	21714	21733	GGAATGCTTTCATAGCTTCC	43	117
725607	2362	2381	61983	62002	TGCTCTCTTTCTCACATACC	35	257
725608	2363	2382	61984	62003	CTGCTCTCTTTCTCACATAC	40	258
725609	2364	2383	61985	62004	ACTGCTCTCTTTCTCACATA	62	259
780133	1	20	3120	3139	TCACCGCCCGCAGCCAGCGC	95	260
780134	56	75	3175	3194	CTGCTCAGGGAACCGGCAGG	134	261
780135	100	119	3219	3238	TGGCACCTGCTTCCAACCCG	115	262
780136	157	176	3276	3295	ACTTCTTCAGAGTTTCCTCG	59	263
780137	166	185	3285	3304	TGACTATCAACTTCTTCAGA	86	264
780138	169	188	3288	3307	GCCTGACTATCAACTTCTTC	59	265
780139	173	192	3292	3311	TTCAGCCTGACTATCAACTT	70	266
780140	176	195	3295	3314	TTGTTCAGCCTGACTATCAA	87	267
780141	203	222	3322	3341	GTTTCTATCTGTTTTCCTTC	44	268
780142	271	290	N/A	N/A	CTTGAAATAACTTGGAGGCG	72	269
780143	315	334	3706	3725	ATAGGAGTCCAAGACGATCA	49	270
780144	362	381	10386	10405	TTGCACAGAAGTGACCAACC	64	271
780145	406	425	10430	10449	GTCCCATTAAGCTTTGCATT	48	272
780146	451	470	N/A	N/A	ATTGGTGAACACCAAGGACT	48	273
780147	495	514	13761	13780	CAAGTTTACACTGGCATTAT	57	274
780148	539	558	13805	13824	CCTGAAGTTAGGAGGAGATC	32	275
780149	585	604	16105	16124	CATGAAAATATCACTTTCTT	76	276
780150	601	620	16121	16140	TGGCATCAAAAATTAACATG	70	277
780151	604	623	16124	16143	GCATGGCATCAAAAATTAAC	96	278
780152	608	627	16128	16147	GAGTGCATGGCATCAAAAAT	44	279
780153	611	630	16131	16150	AATGAGTGCATGGCATCAAA	74	280
780154	629	648	16149	16168	ACTTCATCATTGGCTGGAAA	57	281
780155	673	692	16193	16212	CTCTCTCAAACAGCACATGT	74	282
780156	717	736	18616	18635	ATAATCTTTGTTCTCAACAA	62	283
780157	764	783	18663	18682	ATTTCCTCTTCATCTTTAAA	134	284
780158	808	827	18707	18726	AAGGAATCGCTAGGGAATGT	57	285
780159	852	871	21683	21702	ATAACACCTGACATTGCCAC	48	286
780160	878	897	21709	21728	GCTTTCATAGCTTCCACCAC	60	287
780161	881	900	21712	21731	AATGCTTTCATAGCTTCCAC	59	288

[0574]

780162	885	904	21716	21735	AGGGAATGCTTTCATAGCTT	34	289
780163	888	907	21719	21738	CATAGGGAATGCTTTCATAG	99	290
780164	896	915	21727	21746	CTTTCACTCATAGGGAATGC	34	291
780165	940	959	21771	21790	CTAATGTAAGCCTATGGAGC	51	292
780166	988	1007	27963	27982	CCACAAACTCATGGACTTCG	30	293
780167	1032	1051	28007	28026	GATCTGCAATGCTGCATTCT	58	294
780168	1078	1097	N/A	N/A	TTAAGAAAATAGTCTCAGTG	160	70
780169	1123	1142	29384	29403	CATCATCATTCTCTTGATTC	63	295
780170	1167	1186	29428	29447	TTTGTAACAGGCTTCCAGCC	46	296
780171	1216	1235	N/A	N/A	AGCATGCGGCCTCCTGCACG	73	297
780172	1260	1279	29611	29630	CTCATGTAAACTGTTTTGGT	62	298
780173	1304	1323	31020	31039	ACTTCCCTATGAGCTGGGAA	134	299
780174	1348	1367	31064	31083	GGAAAACTTCCTTTGATGAA	91	300
780175	1417	1436	35364	35383	TTGATAACAGTATTTTTCTG	75	301
780176	1461	1480	35408	35427	TATATGCTTCTGCATTAACT	78	302
780177	1505	1524	35452	35471	TGATTTAGCATTTTACAGCC	106	303
780178	1549	1568	37598	37617	CTGCTGCCATTATATCCAGG	56	304
780179	1598	1617	37647	37666	GGTAATGATGTCTCATGACG	60	305
780180	1645	1664	37694	37713	CAGGCACTATAAAATGTAAA	93	306
780181	1689	1708	41922	41941	CTTATGATGAAATTCTGTAT	60	307
780182	1734	1753	41967	41986	TTTGTGAATATCATTCTTGA	52	308
780183	1779	1798	52693	52712	AATCCCAGGATTTCCAATGA	78	309
780184	1786	1805	52700	52719	ATTTCTGAATCCCAGGATTT	119	310
780185	1789	1808	52703	52722	CACATTTCTGAATCCCAGGA	41	311
780186	1793	1812	52707	52726	AATCCACATTTCTGAATCCC	70	312
780187	1796	1815	52710	52729	TTTAATCCACATTTCTGAAT	80	313
780188	1826	1845	52740	52759	TCAGGAAAATGTACAATAGA	128	314
780189	1873	1892	52787	52806	GAAGCACTGAATCCATAGCA	34	315
780190	1919	1938	N/A	N/A	CCCAGACACTGAATTTCTTG	56	37
780191	1963	1982	53003	53022	TGAACACATTCTTCTTTGTA	64	316
780192	2009	2028	53049	53068	TATAAGCTGGAAACCAGAAT	86	317
780193	2053	2072	N/A	N/A	TCTGAAATCCTTTAGTCTGT	106	318
780194	2097	2116	56031	56050	CAGCTTAGAAAAAGATGCTG	66	319
780195	2141	2160	56075	56094	GACATTTGATGGAATATTAC	45	320
780196	2185	2204	N/A	N/A	AGAGGTTTAGAAACTGTTGA	44	321
780197	2229	2248	56237	56256	TTTTAAGTAATCATCCATAG	70	322
780198	2273	2292	56281	56300	ATGATGCTGTTATTCTGATC	71	323
780199	2317	2336	56325	56344	TTGCTTGATTGGCATCTGCT	41	324
780200	2356	2375	N/A	N/A	CTTTCTCACATACCTGACAA	59	325
780201	2359	2378	N/A	N/A	TCTCTTTCTCACATACCTGA	50	326
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	36	235

표 4

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

[0575]

[0576]

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
693428	2361	2380	61982	62001	GCTCTCTTTCTCACATACCT	28	73
693430	5537	5556	100526	100545	GCCCATTTCTTCAACAGAGT	25	89
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	23	235
780276	4929	4948	93390	93409	CTGTGCCATGATTTTACAAA	62	327
780277	4973	4992	98121	98140	CCCTTAGGGTGTTTTGGACA	65	328
780278	5019	5038	98167	98186	CCTTTTTTTTGAAAGAAATT	154	329
780279	5063	5082	98211	98230	TCTAGGAGCTTAAAATACTG	112	330
780280	5109	5128	98257	98276	AACCAGCAAATATTCTTCTC	83	331
780281	5169	5188	99175	99194	TTCAGAGTTCTCACAATGGG	72	332
780282	5217	5236	99223	99242	CCAAAATCCCATTGGAAAAT	88	333
780283	5261	5280	99267	99286	AGCATGTAAGGTGAAATCTC	88	334
780284	5305	5324	100157	100176	GCCAATACATTCTGTTTGGG	25	335
780285	5349	5368	100201	100220	CAGACAATAAGCTTCAGGAG	82	336
780286	5396	5415	100248	100267	ATTTTTAAGAAACTCTCTGG	86	337
780287	5440	5459	100429	100448	CTTGGCCCAAAAGAATACAG	69	338
780288	5488	5507	100477	100496	GCAACCCAGGAAACCATTCT	83	339
780289	5532	5551	100521	100540	TTTCTTCAACAGAGTTTCTC	157	340
780290	5535	5554	100524	100543	CCATTTCTTCAACAGAGTTT	64	341
780291	5539	5558	100528	100547	ATGCCCATTTCTTCAACAGA	59	342
780292	5542	5561	100531	100550	ATAATGCCCATTTCTTCAAC	135	343
780293	5577	5596	100566	100585	GATTTTTTGATGTTCTTCAC	64	344
780294	5622	5641	N/A	N/A	TAAGAGATCTCCTTCCTCTG	77	345
780295	5666	5685	101304	101323	ATCTGAGATATTGGAATGGT	86	346
780296	5710	5729	101348	101367	ACATAATATTTCTAGGCAGG	48	347
780297	5754	5773	101392	101411	GAGAAACTCTGGAGCTTGTT	138	348
780298	5798	5817	106489	106508	TCATAGGCTGCTCGGTAAAC	109	349
780299	5842	5861	106533	106552	GTGATGTATGTTTATTAAAA	88*	350
780300	5886	5905	113083	113102	GTGGAGGTGGCAAAGCACCA	50*	351
780301	5946	5965	113143	113162	CTCCATCACCAACATCCGGG	121	352
780302	5990	6009	113187	113206	TTGTCCTGCTGAAGCAGGCG	136	353
780303	6034	6053	113231	113250	CGTGGAGTGCAATCCTGTGC	89	354
780304	6078	6097	118411	118430	GTATATAATCATGGCTGAGT	68	355
780305	6122	6141	118455	118474	GGATACAGTGTGAAAAGCAG	61	356
780306	6166	6185	118499	118518	GAGCAATGCCGTAGTCAGCA	61	357
780307	6170	6189	118503	118522	TACTGAGCAATGCCGTAGTC	75	358
780308	6173	6192	118506	118525	CAGTACTGAGCAATGCCGTA	61	359
780309	6175	6194	118508	118527	AGCAGTACTGAGCAATGCCG	58	360
780310	6177	6196	118510	118529	ACAGCAGTACTGAGCAATGC	70	361
780311	6180	6199	118513	118532	TCTACAGCAGTACTGAGCAA	88	362
780312	6211	6230	118544	118563	CTGGTGTGCCCTCTGATGTT	97	363
780313	6255	6274	124886	124905	GTTATAAATGACATTTCCTC	77	364
780314	6299	6318	124930	124949	ATGTCATAGAGTAGTAAACC	111	365

780315	6345	6364	124976	124995	ATTTGGAAACTTCAAACCCT	60	366
780316	6389	6408	N/A	N/A	ACTGGATCAGGTAATTTTCC	62	367
780317	6433	6452	126549	126568	TTAATTTCTCAACCATAGGC	120	368
780318	6477	6496	126593	126612	AGAAGTAGGCCTTTCTTGAG	95	369
780319	6521	6540	129666	129685	AGACAGACTAATTCAGCTGA	78	370
780320	6568	6587	129713	129732	CCATGCATTCAACAATTACG	57	371
780321	6612	6631	129757	129776	GCCCAGCCAAATGCTTGCAT	41	372
780322	6656	6675	129801	129820	TTTAAGTCAAGAAATGAGAG	92	373
780323	6700	6719	132410	132429	ATATTCTACTATCAGCAACT	97	374
780324	6744	6763	132454	132473	CCAGCTTTCCTTTTCAACAG	132	375
780325	6788	6807	132498	132517	GTATTGATGACCAGGAGAGT	92	376
780326	6832	6851	132542	132561	AATCAGTCATCTTTTCTAGG	98	377
780327	6876	6895	N/A	N/A	TTTGCTTTGCTTGGAAAAGG	85	378
780328	6920	6939	134252	134271	GCTAACTTGCCATCAGCGGT	84	379
780329	6964	6983	137368	137387	AAGGAGCAGCTCCTTTAAGC	65	380
780330	7008	7027	137412	137431	ACACATCAATGGAGTACTGA	51	381
780331	7052	7071	137456	137475	CCCCACATTACATTTCTTTC	124	382
780332	7096	7115	137500	137519	TGGTGAAATCATTAGAAAAG	119	383
780333	7141	7160	N/A	N/A	CATAAGAAAACAGTTGGCTT	61	384
780334	7185	7204	141546	141565	AGTGTCTACCACCACTGTTA	124	385
780335	7229	7248	141590	141609	CACACTTCCACAACAGGGCT	116	386
780336	7273	7292	141634	141653	GCACGCAGTCTATTAGTCCA	60	387
780337	7318	7337	142966	142985	GTTTTGATTCCTTGTTTTCT	92	388
780338	7362	7381	143010	143029	CTGAAGGCAGAGGGTTTTCA	78	389
780339	7406	7425	143054	143073	AAAATATGGCCTCCTCCAGT	82	390
780340	7457	7476	143105	143124	CAAAAGTTGTAAATTACACG	77	391
780341	7501	7520	N/A	N/A	TAAGGCTTCCTAGCTGTGCT	89	392
780342	7545	7564	145148	145167	TTCAGTATTTTTCCGGTTGT	121	393
780343	7589	7608	145758	145777	CAAACGGTCAAGCAAGATTG	138	394
780344	7636	7655	145805	145824	CAATGTGTTTTTCTAAATTT	102	395
780345	7688	7707	145857	145876	TCTTACTCAACAGATGTTCG	92	396
780346	7732	7751	145901	145920	GAGGAGAGAATAATTTTCCT	91	397
780347	7776	7795	145945	145964	GAGTACCCTTTCCATGTGAA	34	398
780348	7822	7841	145991	146010	AAAATAATAACATTCCTTCA	96	399
780349	7867	7886	146036	146055	AAAATACACATTTACTGGTA	115	400
780350	7912	7931	146081	146100	CTGGTATTTATAAGAAATAT	91	401
780351	7960	7979	146129	146148	ATTAGGTACTTCACAGATTT	140	402

표 5

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시	서열 번호: 1 중단	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호

[0577]

	부위	부위					
693428	2361	2380	61982	62001	GCTCTCTTTCTCACATACCT	30	73
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	39	235
780352	8004	8023	146173	146192	AACAAAAAATTATCGGCCTT	79	403
780353	8052	8071	146221	146240	CTTAAGCACAGAATTTAAAA	94	404
780354	8096	8115	146265	146284	ATACCGTGCAGATTTCTAGA	91	405
780355	8140	8159	146309	146328	AAGAAGGAATACATTACATG	148	406
780356	8186	8205	146355	146374	TTTGAATATTTACAAGCATA	163	407
780357	8201	8220	146370	146389	ATTAGTGCAAATTCATTTGA	79	408
780358	8206	8225	146375	146394	ACTTTATTAGTGCAAATTCA	118	409
780359	8211	8230	146380	146399	AAAGGACTTTATTAGTGCAA	48	410
780360	8216	8235	146385	146404	CCAACAAAGGACTTTATTAG	75	411
780361	8221	8240	146390	146409	ACATACCAACAAAGGACTTT	98	412
780362	8231	8250	146400	146419	AAGAGAATTCACATACCAAC	164	413
780363	8275	8294	146444	146463	AATTGAGTGAAGTTGTGTAA	133	414
780364	8319	8338	146488	146507	ATGTCATGTTTTTTCATTAG	157	415
780365	8364	8383	146533	146552	AAAGAGAGTTTCTGTGTCTT	146	416
780366	8408	8427	146577	146596	ACAACTCTATTATGTCTAGG	161	417
780367	8452	8471	146621	146640	TATACAAAATTCAGGGTATC	94	418
780368	8515	8534	146684	146703	TAGTGGTATGAATAAAAAAA	107	419
780369	8561	8580	146730	146749	AGATGAATATAAGCATTAGA	98	420
780370	8605	8624	146774	146793	TATCTGAATGATGTAGGATC	118	421
780371	8650	8669	146819	146838	GTAGGAGCTGTGGAATTCTA	125	422
780372	8694	8713	146863	146882	CTTCAGCAACTGAAAAGTGT	132	423
780373	8741	8760	146910	146929	CTAGGGTGGCAGATATTTTT	126	424
780374	8785	8804	146954	146973	TATTGTGGTAAGCTATGTAA	106	425
780375	8829	8848	146998	147017	AAATGACCTCAAATTATTAC	84	426
780376	8873	8892	147042	147061	GGTCAGGGCCAAAGAATTTA	130	427
780377	8917	8936	147086	147105	ACTAGTTGTCCTATCACAGG	81	428
780378	8962	8981	147131	147150	GTTTTCACATAGTAAAATGC	47	429
780379	9006	9025	147175	147194	TCATCTTTAAGAATTTGATT	94	430
780380	9050	9069	147219	147238	ATAACAAGTTAAAGCATAGC	58	431
780381	9094	9113	147263	147282	CTGGAACAAAGAGCTCTATT	97	432
780382	9143	9162	147312	147331	CTTTGGTAAAAAAAAATTGCA	125	433
780383	9183	9202	147352	147371	ATTATTCCATTTAAATATGG	125	434
780384	9188	9207	147357	147376	CCTTTATTATTCCATTTAAA	77	435
780385	9193	9212	147362	147381	AAAAACCTTTATTATTCCAT	93	436
780386	N/A	N/A	82225	82244	CCTCTTTCAGTTTATTGTGA	87	437
780387	N/A	N/A	82365	82384	ATAGTTGACAGGAATTTATA	71	438
780388	N/A	N/A	82505	82524	GTTTAGTGGAAGTATTAAGG	51	439
780389	N/A	N/A	82645	82664	TATATGATAACATCACACAT	106	440
780390	N/A	N/A	82785	82804	TTCCATAGAACACTCTTTAT	219	441
780391	N/A	N/A	82925	82944	AGGAAATTATGCTGTGTTAC	108	442
780392	N/A	N/A	83065	83084	AGAAAAATGGTTTATTTAAG	96	443
780394	N/A	N/A	79043	79062	ACACTGACCATACACAAGCT	100	444

[0578]

780395	N/A	N/A	143142	143161	GCCTAGCTGTGCTGTCATCA	126	445
780396	N/A	N/A	143282	143301	TACCAGTCTTATGTTTCACT	108	446
780397	N/A	N/A	143422	143441	ATTTCCCATTTTTGCCTTAG	62	447
780398	N/A	N/A	143565	143584	TGTATTGCTGCAAGAAAAAA	90	448
780399	N/A	N/A	143705	143724	ACGCAAATATATTTATGCAG	74	449
780400	N/A	N/A	143845	143864	ATGTTCAAAACATTCATTAT	137	450
780401	N/A	N/A	143985	144004	TAATAGTTTACAGTCATTAA	111	451
780402	N/A	N/A	144125	144144	TATAACTTCAGTTATAAGCA	92	452
780403	N/A	N/A	144265	144284	AGACAAGCAAGATCTGGTAG	118	453
780404	N/A	N/A	144405	144424	ACAGGAGCTAACATTTCAAA	123	454
780405	N/A	N/A	144553	144572	AACCGTCTTGGAGTTTATAT	56	455
780406	N/A	N/A	144694	144713	TATACTGATACTATGTCAAA	193	456
780407	N/A	N/A	144834	144853	CAGTATTTATACATTACCCT	150	457
780408	N/A	N/A	144974	144993	TTTTCTAGGTGACCCTTCAA	119	458
780409	N/A	N/A	145168	145187	CCTTTCTGCTTTTGTGTACC	93	459
780410	N/A	N/A	145310	145329	AAGTTCTTTACACTATAAAC	112	460
780411	N/A	N/A	145450	145469	GACATTATGTAGATATAGAT	80	461
780412	N/A	N/A	145597	145616	ATTATTATTTATAAAAAACT	124	462
780413	N/A	N/A	145740	145759	TGTATCTCTAGAAAAAGAAA	111	463
780414	N/A	N/A	3862	3881	AATCACAGTCAGAGGTTCCT	120	464
780415	N/A	N/A	4122	4141	CCCTTTTCCAAACTATTCAT	119	465
780416	N/A	N/A	4157	4176	GTGACAAAGTTGCATTTTAT	108	466
780417	N/A	N/A	4174	4193	TCTACAAGAGTTTGCTAGTG	97	467
780418	N/A	N/A	4185	4204	AAGTGCTGAACTCTACAAGA	134	468
780419	N/A	N/A	6986	7005	CTCTCACTTCGCTATGACAG	116	469
780420	N/A	N/A	7557	7576	AACCGTCAATTTTCTAAAGA	110	470
780421	N/A	N/A	7842	7861	CTATTCAATTAAAAGCTTAT	122	471
780422	N/A	N/A	8002	8021	CTCAAGGAAAAAAACCTGTTT	125	472
780423	N/A	N/A	8263	8282	AAAGGCGGCAATTTCTGATA	130	473
780424	N/A	N/A	8791	8810	TATACTTGACATGGTCAAAA	177	474
780425	N/A	N/A	8820	8839	CTCCAATTCATTCTATTATA	89	475
780426	N/A	N/A	11028	11047	AACATAGCTGGTAAAATTAC	143	476
780427	N/A	N/A	11977	11996	AAACATTCAATGAATAGAAG	86	477
780428	N/A	N/A	12155	12174	ACGGAAGAAATTTTTCTTCA	116	478

표 6

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
693428	2361	2380	61982	62001	GCTCTCTTTCTCACATACCT	38	73
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	18	235

[0579]

780429	N/A	N/A	12244	12263	CCAGTCTTCGATTCTCTGCC	135	479
780430	N/A	N/A	12353	12372	TTGGCTTTACATTATTGGAA	41	480
780431	N/A	N/A	12761	12780	GTGGCCGTTGCTCACGCCTG	130	481
780432	N/A	N/A	12910	12929	TCTTAGACATGTTGATATAT	136	482
780433	N/A	N/A	14791	14810	TCTTAGCAGGACTGATGAGG	75	483
780434	N/A	N/A	15592	15611	CAAATCAATTCATTACCAAG	91	484
780435	N/A	N/A	15874	15893	GCTCTAGATCTTTATAAATG	102	485
780436	N/A	N/A	16258	16277	TACTTTTCCCAGTATAAGCC	114	486
780437	N/A	N/A	16448	16467	CCTTATGCCTTGTTAAGCAA	84	487
780438	N/A	N/A	16899	16918	GAAATTAGACTGGTAAACTG	113	488
780439	N/A	N/A	16920	16939	ATCCCATTCTGGGAACTGCA	61	489
780440	N/A	N/A	17294	17313	TTGTATTCCTTGCAAAATGT	123	490
780441	N/A	N/A	17451	17470	TTAGTTGCAAGATAGAACAT	82	491
780442	N/A	N/A	17796	17815	ATGGTCTAGTTTCCACAGTA	44	492
780443	N/A	N/A	18025	18044	AGTAAGTTCCATTTGGAGTC	61	493
780444	N/A	N/A	18279	18298	GGGAAATTCTAGAGAAAACT	64	494
780445	N/A	N/A	18439	18458	TGTGAAGCAGCCCTTCCTAA	128	495
780446	N/A	N/A	19114	19133	ACTTCAGGTCACACCTTCAT	66	496
780447	N/A	N/A	19502	19521	CACATCAAATTAATTTCTTC	95	497
780448	N/A	N/A	19553	19572	AAACAGAATATGAACCATTA	129	498
			19583	19602			
780449	N/A	N/A	19556	19575	ACAAAACAGAATATGAACCA	71	499
			19586	19605			
780450	N/A	N/A	19559	19578	AAAACAAAACAGAATATGAA	143	500
			19589	19608			
780451	N/A	N/A	19562	19581	TACAAAACAAAACAGAATAT	190	501
			19592	19611			
780452	N/A	N/A	19953	19972	TGTGGATAAGAAAACATTGT	119	502
780453	N/A	N/A	20195	20214	TCTTGACTTTTGCATTATGA	76	503
780454	N/A	N/A	20454	20473	AAATGTTAACTGTTCTTTTT	60	504
			22583	22602			
780455	N/A	N/A	20713	20732	TCAGCTATGACCTGTTTCCT	34	505
780456	N/A	N/A	20716	20735	AAATCAGCTATGACCTGTTT	128	506
780457	N/A	N/A	21493	21512	GTAAAAAATACTATGCTGTT	87	507
780458	N/A	N/A	22339	22358	CAAACATTAACAATTTTGCT	118	508
780459	N/A	N/A	23396	23415	ACCTCTAATAAATTGTGCTG	73	509
780460	N/A	N/A	23640	23659	GCATGGAATAGTAAAGGCCC	61	510
780461	N/A	N/A	23970	23989	ATTGCTAGGTAGAGAACTTA	50	511
780462	N/A	N/A	24452	24471	TCTAATAAATGACCAAGTTA	76	512
780463	N/A	N/A	24633	24652	GAACTTTATATATAGTTATC	92	513
780464	N/A	N/A	24916	24935	CTTGTGGGAAAGCATGAATC	67	514
780465	N/A	N/A	25082	25101	TCCAACAGTTAACGATCATT	51	515
780466	N/A	N/A	25273	25292	GATATAATCATGATACTAGA	57	516
780467	N/A	N/A	25433	25452	CAGTTTTAGTCATATAACAA	108	517
780468	N/A	N/A	25435	25454	TACAGTTTTAGTCATATAAC	155	518
780469	N/A	N/A	25637	25656	ATATGTATATTTATATACAT	171	519
			25667	25686			
			25697	25716			

[0580]

			25727	25746			
780470	N/A	N/A	25640	25659	TAAATATGTATATTTATATA	149	520
			25670	25689			
			25700	25719			
			25730	25749			
			25794	25813			
			25858	25877			
780471	N/A	N/A	25643	25662	GTATAAATATGTATATTTAT	163	521
			25673	25692			
			25703	25722			
			25733	25752			
			25797	25816			
			25861	25880			
780472	N/A	N/A	25646	25665	TGTGTATAAATATGTATATT	96	522
			25676	25695			
			25706	25725			
			25736	25755			
			25800	25819			
			25864	25883			
780473	N/A	N/A	25649	25668	ATCTGTGTATAAATATGTAT	106	523
			25679	25698			
			25709	25728			
			25739	25758			
			25803	25822			
			25867	25886			
780474	N/A	N/A	25652	25671	TACATCTGTGTATAAATATG	138	524
			25682	25701			
			25712	25731			
			25742	25761			
			25806	25825			
			25870	25889			
780475	N/A	N/A	25655	25674	ATATACATCTGTGTATAAAT	179	525
			25685	25704			
			25715	25734			
			25745	25764			
			25809	25828			
			25873	25892			
780476	N/A	N/A	25658	25677	TTTATATACATCTGTGTATA	129	526
			25688	25707			
			25718	25737			
			25748	25767			
			25812	25831			
			25876	25895			
780477	N/A	N/A	25661	25680	ATATTTATATACATCTGTGT	66	527
			25691	25710			
			25721	25740			
			25751	25770			
			25815	25834			

[0581]

			25879	25898			
780478	N/A	N/A	25664	25683	TGTATATTTATATACATCTG	55	528
			25694	25713			
			25724	25743			
			25754	25773			
			25818	25837			
			25882	25901			
780479	N/A	N/A	25755	25774	TTGTATATTTATATACATCT	88	529
			25819	25838			
			25883	25902			
780480	N/A	N/A	25758	25777	TATTTGTATATTTATATACA	164	530
			25822	25841			
			25886	25905			
780481	N/A	N/A	25761	25780	TTATATTTGTATATTTATAT	156	531
			25825	25844			
			25889	25908			
780482	N/A	N/A	25764	25783	TATTTATATTTGTATATTTA	178	532
			25828	25847			
			25892	25911			
780483	N/A	N/A	25767	25786	ATATATTTATATTTGTATAT	96	533
			25831	25850			
			25895	25914			
780484	N/A	N/A	25770	25789	TGTATATATTTATATTTGTA	110	534
			25834	25853			
			25898	25917			
780485	N/A	N/A	25773	25792	AAATGTATATATTTATATTT	102	535
			25837	25856			
			25901	25920			
780486	N/A	N/A	25776	25795	TATAAATGTATATATTTATA	144	536
			25840	25859			
			25904	25923			
780487	N/A	N/A	25779	25798	ATATATAAATGTATATATTT	122	537
			25843	25862			
			25907	25926			
780488	N/A	N/A	25782	25801	TTTATATATAAATGTATATA	106	538
			25846	25865			
			25910	25929			
780489	N/A	N/A	25785	25804	ATATTTATATATAAATGTAT	139	539
			25849	25868			
			25913	25932			
780490	N/A	N/A	25788	25807	TGTATATTTATATATAAATG	98	540
			25852	25871			
780491	N/A	N/A	25791	25810	ATATGTATATTTATATATAA	110	541
			25855	25874			
780492	N/A	N/A	26102	26121	CCATGTTTAGAAGAAATACT	57	542
780493	N/A	N/A	26738	26757	ATTACATAGTTTGGCAAAAC	107	543
780494	N/A	N/A	27287	27306	ACTGCAGAAATATGTACCTT	89	544
780495	N/A	N/A	27387	27406	CACCCCAGGAAGAAGTCCCA	100	545

[0582]

780496	N/A	N/A	27872	27891	GTTAAATTACCTTTAACATA	174	546
780497	N/A	N/A	28186	28205	TCCTTGAAAGTATCCTCTAC	90	547
780498	N/A	N/A	29148	29167	CCATCCTATCCAGATAAATA	137	548
780499	N/A	N/A	29220	29239	AGGTGTGCTTTAGGAGAAGC	34	549
780500	N/A	N/A	32958	32977	TTATTAAGGCAGAACTCCAA	92	550
780501	N/A	N/A	33224	33243	CATCCCAAGTGCCTACAGAC	146	551
780502	N/A	N/A	34124	34143	ACTTTGAAAGTGGCAGAAAA	125	552
780503	N/A	N/A	34685	34704	TTACAGTTATTTTCACAAAG	89	553
780504	N/A	N/A	34756	34775	CAAACATTATAATTTCTATA	195	554
780505	N/A	N/A	34881	34900	TATAAGCATGTGGAGGTATC	90	555

표 7

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
693428	2361	2380	61982	62001	GCTCTCTTTCTCACATACCT	49	73
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	33	235
780506	N/A	N/A	35751	35770	TGCTATGTGCTATACAATTA	75	556
780507	N/A	N/A	36381	36400	CTTACAAGTCTGCAGTTACG	72	557
780508	N/A	N/A	36600	36619	TGCCCAGAATCTACAGAATC	99	558
780509	N/A	N/A	36661	36680	TCCAGGGCTGCAACTGTACA	107	559
780510	N/A	N/A	36909	36928	GTTCTGTGGACACTGAGATA	91	560
780511	N/A	N/A	36965	36984	GCTTTGCTTGTTAACTGAAA	66	561
780512	N/A	N/A	37065	37084	TTTCTCTCAGGTATTTAAGC	74	562
780513	N/A	N/A	37116	37135	GACTTCTTATAAGGTATTTT	65	563
780514	N/A	N/A	37198	37217	GGCTGGTACCCAAACTTGTC	91	564
780515	N/A	N/A	37201	37220	CAAGGCTGGTACCCAAACTT	72	565
780516	N/A	N/A	37303	37322	ACAATCCCAGCAGGTAGGTG	57	566
780517	N/A	N/A	37333	37352	ATCCTTCTGACCTACGATGG	72	567
780518	N/A	N/A	37398	37417	CTTTGAACTCATAAGATAGA	83	568
780519	N/A	N/A	37548	37567	GCTTATTGAAAGACTGATCT	88	569
780520	N/A	N/A	38071	38090	GAAGGAAGAGAACAGGTATG	94	570
780521	N/A	N/A	38396	38415	CGCCTCTCTCACGCTGCCTG	92	571
780522	N/A	N/A	38720	38739	TGCAAACAATTTTAATAAAC	96	572
780523	N/A	N/A	38837	38856	TGACTACCATGGACCTCCAA	83	573
780524	N/A	N/A	38855	38874	CCTTCACTGGGTCTCACTTG	91	574
780525	N/A	N/A	39213	39232	ACTAAGCTGAAACTATGAAT	104	575
780526	N/A	N/A	39521	39540	CTGATTGATTGTTAACTAAC	79	576
780527	N/A	N/A	40301	40320	TTATAAGTAAGTAGATTTGA	111	577
780528	N/A	N/A	40577	40596	AGATTGTTGCACAAATATTT	95	578
780529	N/A	N/A	40733	40752	TACTATTCAAATGGATATAA	116	579

[0583]

780530	N/A	N/A	41316	41335	GAACTATGCTAAAAACACTA	90	580
780531	N/A	N/A	41593	41612	TTTTGTGTGAGTAGGCTGTG	83	581
780532	N/A	N/A	42005	42024	TATATTCAACATACCCTGTT	100	582
780533	N/A	N/A	43265	43284	TACAACATAAATTCTTGCCA	57	583
780534	N/A	N/A	45337	45356	AATCTTACTGTCAATATAGT	101	584
780535	N/A	N/A	45380	45399	TTAAAAGGAAGTAACCATGT	44	585
780536	N/A	N/A	45462	45481	TGGTATCCCTCCTAAGTGCT	55	586
780537	N/A	N/A	45650	45669	CTCTCTTGGCTCCCGACTGC	75	587
780538	N/A	N/A	46047	46066	TACCTTATTTGGAACTCTGC	86	588
780539	N/A	N/A	46543	46562	TTACTTATATGTAATTTGTT	77	589
780540	N/A	N/A	46567	46586	CATCCTGTAAACCTTTTTTA	79	590
780541	N/A	N/A	47702	47721	AAAGATTAAATTAAGCTGCA	121	591
780542	N/A	N/A	47812	47831	ACATTAGGAATCTCACCTCA	71	592
780543	N/A	N/A	48404	48423	CTGAATATAAATATTATCTA	229	593
780544	N/A	N/A	48835	48854	ATGTATAGCTAGAATGAGGA	99	594
780545	N/A	N/A	48873	48892	AGATGCAACTCAAGAAAACT	81	595
780546	N/A	N/A	48947	48966	TATTTATAAAGCACCTATCT	85	596
			50077	50096			
780547	N/A	N/A	50094	50113	AAATTATATCAAATTGATAT	73	597
780548	N/A	N/A	51550	51569	TTTTATAGAGGCTGAGGAGA	98	598
780549	N/A	N/A	52154	52173	GCCAAACTTTAAAGATGCAG	33	599
780550	N/A	N/A	53367	53386	CGAATAAACTCAGCTAGCTG	87	600
780551	N/A	N/A	53543	53562	GACAGTTATTATATATCATG	42	601
780552	N/A	N/A	53603	53622	AAATTTATTCTTAATCTCCC	79	602
780553	N/A	N/A	54774	54793	AAAACAAGTGAATGCTACAG	92	603
780554	N/A	N/A	54886	54905	CTCTTATGATGCTGAGTATC	108	604
780555	N/A	N/A	55333	55352	ATGTTTTAATGAAAGATTGG	86	605
780556	N/A	N/A	55870	55889	TTAACTATAGATATATTGGG	80	606
780557	N/A	N/A	55936	55955	GGCAAAATGAATAAACAGTA	94	607
780558	N/A	N/A	56363	56382	TTGAATATTTACCTGACAAA	107	608
780559	N/A	N/A	56837	56856	AGTGTTACACAACTTTGGCC	120	609
780560	N/A	N/A	56947	56966	GAGGGCTTTAAAGAAAGATA	97	610
780561	N/A	N/A	57738	57757	TGTAGTACAGTTGTATCAGG	84	611
780562	N/A	N/A	57907	57926	TAAACCTAATACATAATCCT	81	612
780563	N/A	N/A	57911	57930	TCTTTAAACCTAATACATAA	102	613
780564	N/A	N/A	59330	59349	ATTAGAACCTACTGGACCTT	89	614
780565	N/A	N/A	60045	60064	TTTTCTCTAAGATATGCCAT	78	615
780566	N/A	N/A	60338	60357	GCTCATAGCAAAATTAAAAG	109	616
780567	N/A	N/A	60503	60522	TTTCATTTAATGTAGCACTG	101	617
780568	N/A	N/A	61046	61065	AGCAACTGAGACTTGGATTT	91	618
780569	N/A	N/A	62829	62848	ACATTTAGTGTGAACAAATG	77	619
780570	N/A	N/A	62985	63004	TGCTAGTGAGTGCATCATAA	120	620
780571	N/A	N/A	63074	63093	TGGATGGGTACTTTTCTCTA	74	621
780572	N/A	N/A	63219	63238	AGGTAGAGAGAGAGTAACAC	92	622
780573	N/A	N/A	63229	63248	ATTTAGAGCTAGGTAGAGAG	93	623
780574	N/A	N/A	63326	63345	TGAGAAATAAAGTGCTATAG	105	624
780575	N/A	N/A	63342	63361	TGAATGGTAGTATATGTGAG	84	625
780576	N/A	N/A	63662	63681	ACATTGTGAGGTCAAAAAAG	98	626

[0584]

780577	N/A	N/A	64157	64176	TCCCTCTCCAATGGGCCCAC	74	627
780578	N/A	N/A	64433	64452	TTCCAGAGTAATATGTTATG	134	628
780579	N/A	N/A	64500	64519	GATAAACCCCAAGAAGGCAA	76	629
780580	N/A	N/A	64878	64897	TACATTATGTATTAGCTCTA	76	630
780581	N/A	N/A	65152	65171	GTGTTCAAGTCATAGAAATG	88	631
780582	N/A	N/A	65840	65859	AACCAATTAGTATAACATTT	75	632

표 8

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
693428	2361	2380	61982	62001	GCTCTCTTTCTCACATACCT	39	73
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	30	235
780583	N/A	N/A	66279	66298	CTCATTTTTTGCCCTCTCAA	55	633
780584	N/A	N/A	66413	66432	TAATTTTCAAAGCGCATGAA	66	634
780585	N/A	N/A	66417	66436	ATGTTAATTTTCAAAGCGCA	39	635
780586	N/A	N/A	66480	66499	GAAGAAACTTTTTTGGATAA	72	636
780587	N/A	N/A	68762	68781	AATAAATTTGGCAACTTATA	126	637
780588	N/A	N/A	68885	68904	GAGAAAGTAACACAAACAAT	106	638
780589	N/A	N/A	69914	69933	CAAATCCTCAATTACAACTT	91	639
780590	N/A	N/A	69919	69938	ACCAACAAATCCTCAATTAC	98	640
780591	N/A	N/A	70220	70239	GGAGATAGAGATCAACATTT	55	641
780592	N/A	N/A	70279	70298	AATTAAGGGCCATATACATA	79	642
780593	N/A	N/A	72795	72814	ACCCAATTATGAGGATAAAA	41	643
780594	N/A	N/A	72902	72921	TCATTTATTGGAGAAGAGGA	115	644
780595	N/A	N/A	73395	73414	AAACCAAACTATGGAGTTTA	89	645
780596	N/A	N/A	75173	75192	AAGTCCTGTCCTCAAAGAGT	74	646
780597	N/A	N/A	75176	75195	AACAAGTCCTGTCCTCAAAG	99	647
780598	N/A	N/A	75470	75489	AACAAACAAAGTGCCATCTA	52	648
780599	N/A	N/A	75646	75665	ATTATAGAGGCTTATTAACC	83	649
780600	N/A	N/A	76096	76115	TAGAGTTGAAAGCTTCCTTC	65	650
780601	N/A	N/A	76298	76317	CCATCTGAGGAACTTAAGTC	67	651
780602	N/A	N/A	76349	76368	GTCAAACTCTTCAGAGTCTG	24	652
780603	N/A	N/A	76970	76989	TATATAGTATATATATAATA	138	653
			76997	77016			
780604	N/A	N/A	76973	76992	TTATATATAGTATATATATA	104	654
			77000	77019			
780605	N/A	N/A	76976	76995	GTATTATATATAGTATATAT	106	655
			77003	77022			
780606	N/A	N/A	76979	76998	TAAGTATTATATATAGTATA	105	656
			77006	77025			

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780607	N/A	N/A	76982	77001	TAATAAGTATTATATATAGT	76	657
			77009	77028			
780608	N/A	N/A	76985	77004	ATATAATAAGTATTATATAT	78	658
			77012	77031			
780609	N/A	N/A	76988	77007	TATATATAATAAGTATTATA	126	659
			77015	77034			
780610	N/A	N/A	77524	77543	TTTCATAGTTTTATAGCATT	72	660
780611	N/A	N/A	77611	77630	GTCTTATAGTTGGGAACGAA	43	661
780612	N/A	N/A	78065	78084	ACTATCATTTTAACCTCTGA	71	662
780613	N/A	N/A	78080	78099	ACAGTAGGCCAAGTAACTAT	80	663
780614	N/A	N/A	78344	78363	AAGTGATGATAATAATTTGC	54	664
780615	N/A	N/A	78724	78743	TGGCCAATATTCAGGAGGGT	81	665
780616	N/A	N/A	78787	78806	GCTTTGCTTACTAGTGAGTG	70	666
780617	N/A	N/A	81581	81600	GTTTGAAGGAATAGCTGACA	60	667
			87838	87857			
780618	N/A	N/A	81584	81603	AGTGTTTGAAGGAATAGCTG	52	668
			87841	87860			
780619	N/A	N/A	81587	81606	CATAGTGTTTGAAGGAATAG	129	669
			87844	87863			
780620	N/A	N/A	81590	81609	AGCCATAGTGTTTGAAGGAA	40	670
			87847	87866			
780621	N/A	N/A	81593	81612	AAAAGCCATAGTGTTTGAAG	91	671
			87850	87869			
780622	N/A	N/A	81596	81615	CTAAAAAGCCATAGTGTTTG	85	672
			87853	87872			
780623	N/A	N/A	81599	81618	ATTCTAAAAAGCCATAGTGT	117	673
			87856	87875			
780624	N/A	N/A	81630	81649	GCAGCATCATGCAAGCAGCA	31	674
			87887	87906			
780625	N/A	N/A	81633	81652	ATTGCAGCATCATGCAAGCA	81	675
			87890	87909			
780626	N/A	N/A	83145	83164	TGGCGGAATGCAGAAATTTA	61	676
780627	N/A	N/A	83842	83861	GTGGGAAGGAAGAAATGTGC	70	677
780628	N/A	N/A	84184	84203	AGCATATTAATGCCAAATAT	73	678
780629	N/A	N/A	84201	84220	AAAGGCAAATGACACACAGC	87	679
780630	N/A	N/A	84266	84285	ATTAGTCTGGCTAAGAAGAA	95	680
780631	N/A	N/A	84723	84742	ACAGAGCTGAGGTCTGCAAC	58	681
780632	N/A	N/A	84951	84970	AAGCTCAGGAGTTCAGAAAA	111	682
780633	N/A	N/A	86880	86899	GGTTTCTGGATATTAGAACA	76	683
780634	N/A	N/A	87013	87032	TTGTCAGCAACCGATCAAAG	82	684
780635	N/A	N/A	88098	88117	CAATTTGGAGTCTACAATGA	78	685
780636	N/A	N/A	88353	88372	AAATGTAACCTTACGACATT	77	686
780637	N/A	N/A	88867	88886	TAATGCTAACAGCAACAAGG	85	687
780638	N/A	N/A	89084	89103	TCACCTTTACCCTTGTGATT	57	688
780639	N/A	N/A	89635	89654	CAGGCCAAATAGGACTCTAT	51	689
780640	N/A	N/A	89998	90017	AGTCATATTAGTTTCTAATT	96	690
780641	N/A	N/A	90808	90827	CTGCTCTGCTAATGGGCTGG	54	691
780642	N/A	N/A	91043	91062	TTCATGTATCTCTTAACCCA	42	692

[0586]

780643	N/A	N/A	91084	91103	ACTTCCATATTTACCTGCAA	105	693
780644	N/A	N/A	92608	92627	TGCACTAAACTCATTTGACA	98	694
780645	N/A	N/A	92700	92719	GCATCATCTCAGGGAGCCAT	45	695
780646	N/A	N/A	92957	92976	CAGCATATCTCAGCATACCT	51	696
780647	N/A	N/A	93284	93303	CAAACAGTGAAACATGGAAT	89	697
780648	N/A	N/A	93697	93716	TTCAATTGACTAATTCAGTA	85	698
780649	N/A	N/A	94459	94478	GCTGATTGCAATGTTTCAAT	33	699
780650	N/A	N/A	94553	94572	AAATCACATTATCCATGACA	78	700
780651	N/A	N/A	95499	95518	AATAGCTGTCAGACAAGTTG	64	701
780652	N/A	N/A	95576	95595	TTAGAGCTTCTGCACCATGA	91	702
780653	N/A	N/A	95725	95744	TTCCACCTGATTAATTGAAT	70	703
780654	N/A	N/A	96460	96479	ATTTTTTAAAGAGTTTGTGC	51	704
780655	N/A	N/A	96720	96739	TATAAACTCATAGGCCCTGG	74	705
780656	N/A	N/A	97174	97193	GTTTAAGGAATACTTAAACA	81	706
780657	N/A	N/A	97323	97342	TGCCCTGAGAATGAAATAAC	73	707
780658	N/A	N/A	97591	97610	TTTGATGGATTCTACTTGCA	83	708
780659	N/A	N/A	97610	97629	CTCAAAGTAACTACTGCATT	46	709

표 9

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
693428	2361	2380	61982	62001	GCTCTCTTTCTCACATACCT	38	73
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	27	235
780660	N/A	N/A	99313	99332	TCTAAAAATCTAATAAGTCT	89	710
780661	N/A	N/A	99451	99470	TACTCCAAGGTTTTATGAGC	81	711
780662	N/A	N/A	99569	99588	AAGAGATAATTACAGTCCCT	71	712
780663	N/A	N/A	99813	99832	CTAAACGCAAAACTTTCTGA	107	713
780664	N/A	N/A	100778	100797	TAGAATACAAGATTTTATTG	134	714
780665	N/A	N/A	102009	102028	TGAGCACCTAAACATGCTAC	65	715
780666	N/A	N/A	102270	102289	ACAGCATCGCAGGTCTTGTA	50	716
780667	N/A	N/A	102579	102598	AATGCATTTCATAGTTGTCC	60	717
780668	N/A	N/A	104248	104267	TTCTCTATTTGAGAATCGCC	64	718
780669	N/A	N/A	104621	104640	AAATTTCAAGTTGGAGTAGG	85	719
780670	N/A	N/A	105660	105679	GTCATATAGTGGCCCCTAAA	31	720
780671	N/A	N/A	106100	106119	CACTGGTATGCCCTTCCAAC	65	721
780672	N/A	N/A	106561	106580	GAATTTCTTACTTGTCTTAA	95	722
780673	N/A	N/A	107953	107972	GCTACATAAAATAAATCACC	79	723
780674	N/A	N/A	109817	109836	AGAGTCTGAAGTATCTAGAA	98	724
780675	N/A	N/A	110040	110059	TGAAGCCTGGAACCAGTTTA	94	725
780676	N/A	N/A	110227	110246	CCTAAAGCCAATTAGCACAA	101	726

[0587]

780677	N/A	N/A	110637	110656	AGTGTAGCCACTAAGAATTT	88	727
780678	N/A	N/A	110978	110997	CTTATACACTAATTGGCTCT	66	728
780679	N/A	N/A	111011	111030	TTTCTTCCACCATTCCCTTA	101	729
780680	N/A	N/A	111182	111201	CTCACTAATTGCAAAGAAAA	109	730
780681	N/A	N/A	111343	111362	CAAAGCTTCAGACTGTGATC	70	731
780682	N/A	N/A	111843	111862	TCAGAGAGGCCCGCCATGGG	122	732
780683	N/A	N/A	111897	111916	TTCACATGGCTGAAGTCTTG	115	733
780684	N/A	N/A	112310	112329	ATCTACTGAATTCTGGTTAG	103	734
780685	N/A	N/A	112349	112368	GCACACAGTGTAGTCATACT	44	735
780686	N/A	N/A	114870	114889	AACCCAAGATTCCCCCTGGT	99	736
780687	N/A	N/A	115427	115446	TGGAGAAGTAAGCTAACAGT	109	737
780688	N/A	N/A	115958	115977	TAACTGAAAATTCAAGCCTG	115	738
780689	N/A	N/A	116039	116058	CTTAAGGAAAATGAGCTCTC	106	739
780690	N/A	N/A	116174	116193	TATAATATCTAGCTTTCCCT	95	740
780691	N/A	N/A	116253	116272	CAGAGGGAGAAAAACACTGA	110	741
780692	N/A	N/A	116357	116376	CCCTTGAGGGTGTCACAATC	82	742
780693	N/A	N/A	116374	116393	ATCTTTGTATCTCTGCTCCC	89	743
780694	N/A	N/A	116669	116688	TTGAAATAATAAGTAAAGAT	123	744
780695	N/A	N/A	116874	116893	ATAAGACATGCCTCTTTAAG	74	745
780696	N/A	N/A	117178	117197	AGTACATATTATTTAACTGC	61	746
780697	N/A	N/A	117306	117325	ACTGTTGGTTTTGGCTCACA	66	747
780698	N/A	N/A	117646	117665	TCTGGAGACTGACCCACGCA	73	748
780699	N/A	N/A	118398	118417	GCTGAGTGGAGGTATCTGCC	92	749
780700	N/A	N/A	119907	119926	ATATGGTTTAGGAGAGACTA	41	750
780701	N/A	N/A	121039	121058	ATACTTAACTCATGGATAGA	80	751
780702	N/A	N/A	121425	121444	AAAAGTGCAATTGCCATAGG	57	752
780703	N/A	N/A	121530	121549	CCGGTAACATTTTATTTACC	62	753
780704	N/A	N/A	121871	121890	TCAATGTATTGTTGCCAAAT	45	754
780705	N/A	N/A	122553	122572	ATGAGCTACCCACACAGTCA	78	755
780706	N/A	N/A	123081	123100	TTGGAAGGATGGAGACATCG	28	756
780707	N/A	N/A	123885	123904	TGATATGGCATGATGTCTAC	67	757
780708	N/A	N/A	124062	124081	AGATGATATGCTATGACATA	77	758
780709	N/A	N/A	124679	124698	TGTCCTGTCTCATAACATCT	68	759
780710	N/A	N/A	125144	125163	AGAATATTTATGCACTAAAC	71	760
780711	N/A	N/A	125277	125296	GTTCTAACAGCAATTTCCTT	78	761
780712	N/A	N/A	126145	126164	ATCCTTATGTCCTCACAGAT	89	762
780713	N/A	N/A	126446	126465	TATTTCCTCTCAATGTTTAT	125	763
780714	N/A	N/A	127216	127235	TTAAAAAAAGGAATGGGATA	92	764
780715	N/A	N/A	127242	127261	CAACCTGAAAAAATTAGTCT	79	765
780716	N/A	N/A	127360	127379	ATAAATGAGTTGATCAGTGG	83	766
780717	N/A	N/A	127443	127462	TATTCCTGGATGAGAAAAAT	103	767
780718	N/A	N/A	127460	127479	CCTAAGACTGGTTAAAATAT	91	768
780719	N/A	N/A	128188	128207	ATAAGGAAAGTTGTTCTGGG	108	769
780720	N/A	N/A	132660	132679	ATGCAATAACAATTATGCAC	75	770
780721	N/A	N/A	133278	133297	GGAGTTGATATTTCAGGTAC	81	771
780722	N/A	N/A	134443	134462	TTTTCAGAGGATCTACTGTG	90	772
780723	N/A	N/A	136265	136284	TAAATGTGAGGAAATATTTG	94	773
780724	N/A	N/A	137896	137915	CATATGTATAGTCCGTGAAT	81	774

[0588]

780725	N/A	N/A	138142	138161	TCACTGAGGAATGTGATAAA	108	775
780726	N/A	N/A	138369	138388	TTTATTGACAGCTTACCAGG	83	776
780727	N/A	N/A	138502	138521	AGCAAAAAACAAAGGAGTCA	94	777
780728	N/A	N/A	138562	138581	GAGAACAGTGAGAAGTACAA	100	778
780729	N/A	N/A	138891	138910	TAGAGATCTGAGTCAATTTC	70	779
780730	N/A	N/A	139058	139077	GCTACTGTGAAGGAAAACAT	66	780
780731	N/A	N/A	139370	139389	ATCCAAATGTTAACCACATA	60	781
780732	N/A	N/A	139871	139890	ACAGGAGATACTTGTTCAGA	62	782
780733	N/A	N/A	140263	140282	TAGAAAATAGTTCCAATTAG	86	783
780734	N/A	N/A	140887	140906	CCTTAAAATATTTCCCTTTC	115	784
780735	N/A	N/A	141689	141708	AAAGATAATTCTTTTGGGAA	129	785
780736	N/A	N/A	144735 144754	144754 144773	GTACAAATATGAGTATTTAG	65	786

[0589]

[0590] **실시예 4: 인간 LRRK2 RNA 발현 *시험관내*, 단일 용량에서 혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머의 효과**

[0591] 인간 LRRK2 핵산에 상보성인 변형된 올리고뉴클레오타이드는 *시험관내* LRRK2 RNA에서 그것의 효과에 대하여 설

계 및 시험되었다. 변형된 올리고뉴클레오타이드는 유사한 배양 조건을 가졌던 일련의 실험에서 시험되었다.

[0592] 20,000 세포/웰의 밀도에서 배양된 SH-SY5Y 세포는 미처리된 대조군에 대하여 4,000 nM 농도의 변형된 올리고뉴클레오타이드로 또는 변형된 올리고뉴클레오타이드 없이 전기천공을 사용하여 형질감염되었다. 대략 24 시간 후, RNA는 세포로부터 단리되었고 LRRK2 RNA 수준은 실시예 2에서 기재된 바와 같이 인간 프라이머 프로브 세트 RTS3132를 사용하여 정량적 실시간 PCR에 의해 측정되었다. LRRK2 RNA 수준은, RIBOGREEN®에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다. 결과는 미처리된 대조군 세포에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다. 별표 (*)로 표시된 퍼센트 대조군 값을 가진 변형된 올리고뉴클레오타이드는 프라이머 프로브 세트의 앰플리콘 영역을 표적화한다. 추가의 검정은 앰플리콘 영역을 표적화하는 올리고뉴클레오타이드의 효력 및 효능을 측정하는데 사용될 수 있다.

[0593] 표 10-50에서 변형된 올리고뉴클레오타이드는 5-10-5 MOE 갭머이다. 갭머는 20개의 핵염기 길이이고, 여기서 중심 갭 단편은 10개의 2'-데옥시뉴클레오사이드를 포함하고, 5개의 2'-MOE 뉴클레오사이드를 포함하는 5' 말단 및 3' 말단 둘 모두에서 윙 단편에 의해 측접된다. 갭머용 당 모티프는 (5'부터 3'까지) 하기이고: eeeeeddddddddddeeeee; 여기서 'd'는 2'-데옥시리보오스 당을 나타내고 'e'는 2-MOE 변형된 당을 나타낸다. 각 갭머 전반에 걸쳐 모든 시토신 잔기는 5-메틸 시토신이다. 각 갭머용 인터뉴클레오사이드 연결기는 혼합된 포스포디에스테르 및 포스포로티오에이트 연결기이다. 갭머용 인터뉴클레오사이드 연결기 모티프는 (5'부터 3'까지) 하기이고: soooosssssssssssooss; 여기서 'o'는 포스포디에스테르 인터뉴클레오사이드 연결기를 나타내고 's'는 포스포로티오에이트 인터뉴클레오사이드 연결기를 나타낸다. "개시 부위"는 갭머가 인간 핵산 서열에서 상보성인 5'-최말단 뉴클레오사이드를 나타낸다. "중단 부위"는 갭머가 인간 핵산 서열에서 상보성인 3'-최말단 뉴클레오사이드를 나타낸다.

[0594] 표 10-50에서 열거된 각 변형된 올리고뉴클레오타이드는, 명시된 바와 같이, 인간 LRRK2 핵산 서열 서열번호: 1 또는 서열번호: 2에 상보성이다. 'N/A'는 변형된 올리고뉴클레오타이드가 100% 상보성을 가진 그 특정 핵산 서열에 상보성이지 않다는 것을 나타낸다. 아래 나타난 바와 같이, 인간 LRRK2 RNA의 서열에 상보성인 변형된 올리고뉴클레오타이드는 인간 LRRK2 RNA의 양을 감소시켰다.

표 10

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
693426	185	204	3304	3323	TCCTGGACATTGTTCAGCCT	39	55
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	19	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	37	235
802613	10	29	3129	3148	GAGCTCAGCTCACCGCCCGC	99	787
802614	33	52	3152	3171	GCCGGCCACAGCTCCCCGGG	138	788
802615	80	99	3199	3218	CCGCCCTCCCAGCATGAACG	89	789
802616	89	108	3208	3227	TCCAACCCGCCGCCCTCCCA	122	790
802617	109	128	3228	3247	TAGCCATGGTGGCACCTGCT	68	791
802618	118	137	3237	3256	AGCTGCCACTAGCCATGGTG	126	792
802619	127	146	3246	3265	ACCCCTGACAGCTGCCACTA	83	793
802620	136	155	3255	3274	CCTCTTCGCACCCCTGACAG	106	794
802621	198	217	3317	3336	TATCTGTTTTCCTTCCTGGA	67	795
802622	199	218	3318	3337	CTATCTGTTTTCCTTCCTGG	46	796
802623	200	219	3319	3338	TCTATCTGTTTTCCTTCCTG	50	797
802624	201	220	3320	3339	TTCTATCTGTTTTCCTTCCT	42	798
802625	202	221	3321	3340	TTTCTATCTGTTTTCCTTCC	69	799
802626	204	223	3323	3342	CGTTTCTATCTGTTTTCCTT	46	800
802627	222	241	3341	3360	CTCCAGGATTTGGACCAGCG	45	801
802628	231	250	3350	3369	CAGCAGATCCTCCAGGATTT	91	802
802629	240	259	3359	3378	CGTGAACACCAGCAGATCCT	68	803
802630	280	299	3671	3690	TATTTTTGCCTTGAAATAAC	104	804
802631	289	308	3680	3699	GCACATGGATATTTTTGCCT	38	805
802632	298	317	3689	3708	TCAACAGAGGCACATGGATA	60	806
802633	324	343	3715	3734	GACTCTCATATAGGAGTCCA	124	807
802634	333	352	3724	3743	CACACTCGCGACTCTCATAT	109	808
802635	342	361	N/A	N/A	CACCTGCTGCACACTCGCGA	58	809
802636	351	370	N/A	N/A	TGACCAACCCACCTGCTGCA	101	810
802637	371	390	10395	10414	TCTATTAATTTGCACAGAAG	104	811
802638	380	399	10404	10423	GGACAGACTTCTATTAATTT	61	812
802639	389	408	10413	10432	ATTGTACCTGGACAGACTTC	53	813
802640	426	445	10450	10469	ATCATTTCCAACATCCTGGG	82	814
802641	435	454	10459	10478	GACTTCCCAATCATTTCCAA	98	815
802642	460	479	N/A	N/A	TAAGAATCAATTGGTGAACA	62	816
802643	469	488	13735	13754	TTAGCATTTTAAGAATCAAT	49	817
802644	480	499	13746	13765	ATTATGAACTGTTAGCATTT	47	818
802645	504	523	13770	13789	AATCACTGACAAGTTTACAC	74	819
802646	513	532	13779	13798	CTTCAGTCCAATCACTGACA	54	820
802647	522	541	13788	13807	ATCTAAGGTCTTCAGTCCAA	80	821

[0595]

802648	534	553	13800	13819	AGTTAGGAGGAGATCTAAGG	106	822
802649	535	554	13801	13820	AAGTTAGGAGGAGATCTAAG	96	823
802650	536	555	13802	13821	GAAGTTAGGAGGAGATCTAA	87	824
802651	537	556	13803	13822	TGAAGTTAGGAGGAGATCTA	94	825
802652	538	557	13804	13823	CTGAAGTTAGGAGGAGATCT	58	826
802653	540	559	13806	13825	ACCTGAAGTTAGGAGGAGAT	41	827
802654	541	560	13807	13826	TACCTGAAGTTAGGAGGAGA	53	828
802655	542	561	13808	13827	TTACCTGAAGTTAGGAGGAG	33	829
802656	543	562	N/A	N/A	TTTACCTGAAGTTAGGAGGA	55	830
802657	544	563	N/A	N/A	TTTTACCTGAAGTTAGGAGG	56	831
802658	548	567	N/A	N/A	GTGATTTTACCTGAAGTTAG	53	832
802659	557	576	16077	16096	ATCAGCAAGGTGATTTTACC	61	833
802660	566	585	16086	16105	TCATCCAATATCAGCAAGGT	78	834
802661	575	594	16095	16114	TCACTTTCTTCATCCAATAT	53	835
802662	602	621	16122	16141	ATGGCATCAAAAATTAACAT	47	836
802663	603	622	16123	16142	CATGGCATCAAAAATTAACA	40	837
802664	605	624	16125	16144	TGCATGGCATCAAAAATTAA	75	838
802665	607	626	16127	16146	AGTGCATGGCATCAAAAATT	56	839
802666	609	628	16129	16148	TGAGTGCATGGCATCAAAAA	68	840
802667	610	629	16130	16149	ATGAGTGCATGGCATCAAAA	62	841
802668	612	631	16132	16151	AAATGAGTGCATGGCATCAA	54	842
802669	613	632	16133	16152	GAAATGAGTGCATGGCATCA	49	843
802670	620	639	16140	16159	TTGGCTGGAAATGAGTGCAT	42	844
802671	638	657	16158	16177	AGTTTCTGGACTTCATCATT	95	845
802672	647	666	16167	16186	TTGCATCCAAGTTTCTGGAC	70	846
802673	656	675	16176	16195	TGTAAAGCTTTGCATCCAAG	73	847
802674	682	701	N/A	N/A	CCTCTGAGACTCTCTCAAAC	41	848
802675	691	710	18590	18609	TCAGTTGCTCCTCTGAGACT	51	849
802676	700	719	18599	18618	CAAATTCAGTCAGTTGCTCC	69	850
802677	726	745	18625	18644	CAATATCATATAATCTTTGT	101	851
802678	735	754	18634	18653	CGCACTTAACAATATCATAT	34	852
802679	744	763	18643	18662	ATTTGTTAACGCACTTAACA	63	853
802680	753	772	18652	18671	ATCTTTAAAATTTGTTAACG	136	854
802681	773	792	18672	18691	TGAAGCACAATTTCCTCTTC	51	855
802682	782	801	18681	18700	TGCAGCACATGAAGCACAAT	67	856
802683	791	810	18690	18709	TGTAAACAATGCAGCACATG	77	857
802684	817	836	N/A	N/A	CATTATTGCAAGGAATCGCT	58	858
802685	826	845	N/A	N/A	GGACTTCCACATTATTGCAA	32	859
802686	835	854	21666	21685	CACTCATGAGGACTTCCACA	34	860
802687	861	880	21692	21711	CACAATATTATAACACCTGA	50	861
802688	879	898	21710	21729	TGCTTTCATAGCTTCCACCA	32	862

표 11

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

[0596]

[0597]

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	42	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	17	235
802689	880	899	21711	21730	ATGCTTTCATAGCTTCCACC	24	863
802690	882	901	21713	21732	GAATGCTTTCATAGCTTCCA	36	864
802691	884	903	21715	21734	GGGAATGCTTTCATAGCTTC	30	865
802692	886	905	21717	21736	TAGGGAATGCTTTCATAGCT	36	866
802693	887	906	21718	21737	ATAGGGAATGCTTTCATAGC	44	867
802694	889	908	21720	21739	TCATAGGGAATGCTTTCATA	53	868
802695	890	909	21721	21740	CTCATAGGGAATGCTTTCAT	44	869
802696	891	910	21722	21741	ACTCATAGGGAATGCTTTCA	25	870
802697	892	911	21723	21742	CACTCATAGGGAATGCTTTC	48	871
802698	893	912	21724	21743	TCACTCATAGGGAATGCTTT	29	872
802699	894	913	21725	21744	TTCACTCATAGGGAATGCTT	41	873
802700	895	914	21726	21745	TTTCACTCATAGGGAATGCT	19	874
802701	897	916	21728	21747	TCTTTCACTCATAGGGAATG	27	875
802702	898	917	21729	21748	TTCTTTCACTCATAGGGAAT	40	876
802703	899	918	21730	21749	ATTCTTTCACTCATAGGGAA	35	877
802704	900	919	21731	21750	AATTCTTTCACTCATAGGGA	40	878
802705	901	920	21732	21751	GAATTCTTTCACTCATAGGG	30	879
802706	905	924	21736	21755	TCTTGAATTCTTTCACTCAT	43	880
802707	915	934	21746	21765	GCAACTCACTTCTTGAATTC	53	881
802708	924	943	21755	21774	GAGCAAACAGCAACTCACTT	71	882
802709	949	968	N/A	N/A	AAAAATTACCTAATGTAAGC	112	883
802710	958	977	27933	27952	GGATATTGAAAAAATTACCT	55	884
802711	967	986	27942	27961	TTAATACCAGGATATTGAAA	88	885
802712	989	1008	27964	27983	ACCACAAACTCATGGACTTC	42	886
802713	990	1009	27965	27984	CACCACAAACTCATGGACTT	34	887
802714	991	1010	27966	27985	TCACCACAAACTCATGGACT	45	888
802715	992	1011	27967	27986	TTCACCACAAACTCATGGAC	61	889
802716	993	1012	27968	27987	TTTCACCACAAACTCATGGA	45	890
802717	998	1017	27973	27992	ACAGCTTTCACCACAAACTC	35	891
802718	1007	1026	27982	28001	TACTGCTGCACAGCTTTCAC	40	892
802719	1016	1035	27991	28010	TTCTCTGGGTACTGCTGCAC	47	893
802720	1055	1074	28030	28049	AGGGCCAAACAGCTGAGCGC	70	894
802721	1064	1083	N/A	N/A	TCAGTGAGGAGGGCCAAACA	83	895
802722	1090	1109	29351	29370	CTAAATCTTGATTTAAGAAA	134	896
802723	1099	1118	29360	29379	TCTTTTCCTCTAAATCTTGA	55	897
802724	1111	1130	29372	29391	CTTGATTCTCATTCTTTTCC	47	898
802725	1132	1151	29393	29412	CTTCCCCCTCATCATCATTC	58	899
802726	1141	1160	29402	29421	ATTTATCTTCTTCCCCCTCA	43	900
802727	1150	1169	29411	29430	GCCAAAACAATTTATCTTCT	44	901
802728	1176	1195	29437	29456	CGTTAATGCTTTGTAACAGG	26	902

802729	1194	1213	29455	29474	CTTGTTCTTTCTATGCCACG	64	903
802730	1225	1244	29576	29595	TTAGTGCCCAGCATGCGGCC	37	904
802731	1234	1253	29585	29604	GGAGATTATTTAGTGCCCAG	20	905
802732	1243	1262	29594	29613	GGTACATAAGGAGATTATTT	30	906
802733	1269	1288	29620	29639	TCCAATCTTCTCATGTAAAC	99	907
802734	1278	1297	29629	29648	ATCTTCATCTCCAATCTTCT	93	908
802735	1287	1306	N/A	N/A	GAAATGGCCATCTTCATCTC	110	909
802736	1313	1332	31029	31048	GAGAGCATCACTTCCCTATG	47	910
802737	1322	1341	31038	31057	ATCAGCATGGAGAGCATCAC	48	911
802738	1331	1350	31047	31066	GAAGAATGCATCAGCATGGA	58	912
802739	1357	1376	31073	31092	CAGATGCCTGGAAAACTTCC	51	913
802740	1366	1385	31082	31101	ATGCATTCGCAGATGCCTGG	43	914
802741	1375	1394	31091	31110	GAGTTGACAATGCATTCGCA	59	915
802742	1385	1404	31101	31120	TGTTCTAAGAGAGTTGACAA	85	916
802743	1426	1445	35373	35392	GTATTCCTTTTGATAACAGT	24	917
802744	1435	1454	35382	35401	CATTCAGGTGTATTCCTTTT	27	918
802745	1444	1463	35391	35410	ACTCCAAAACATTCAGGTGT	40	919
802746	1470	1489	35417	35436	AGGAGAATGTATATGCTTCT	18	920
802747	1479	1498	35426	35445	AGCCACTTCAGGAGAATGTA	27	921
802748	1488	1507	35435	35454	GCCACTTTCAGCCACTTCAG	21	922
802749	1514	1533	35461	35480	TCAAAAAGATGATTTAGCAT	113	923
802750	1523	1542	N/A	N/A	TTGCTTCCTTCAAAAAGATG	78	924
802751	1533	1552	N/A	N/A	CAGGGAAGTGTTGCTTCCTT	53	925
802752	1574	1593	37623	37642	ATAACTGTTAGTATTTTGGG	34	926
802753	1607	1626	37656	37675	AGCTGCACTGGTAATGATGT	57	927
802754	1631	1650	37680	37699	TGTAAAATAGCTCGAAGCGC	90	928
802755	1654	1673	N/A	N/A	CTGGCATGCCAGGCACTATA	62	929
802756	1663	1682	N/A	N/A	TGGATTCTTCTGGCATGCCA	40	930
802757	1672	1691	41905	41924	TATCCTCCCTGGATTCTTCT	69	931
802758	1699	1718	41932	41951	CCATATTTAGCTTATGATGA	20	932
802759	1708	1727	41941	41960	GTTTTTTAACCATATTTAGC	38	933
802760	1717	1736	41950	41969	TGAAACACTGTTTTTTAACC	48	934
802761	1743	1762	41976	41995	TAGGACCAGTTTGTGAATAT	72	935
802762	1752	1771	41985	42004	CAAAGCTGCTAGGACCAGTT	69	936
802763	1761	1780	N/A	N/A	GAACCTGTTCAAAGCTGCTA	47	937
802764	1770	1789	N/A	N/A	ATTTCCAATGAACCTGTTCA	71	938
802765	1784	1803	52698	52717	TTCTGAATCCCAGGATTTCC	38	939

표 12

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시	서열 번호: 1 중단	서열 번호: 2 개시	서열 번호: 2 중단	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호

[0598]

[0599]

	부위	부위	부위	부위			
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	42	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	50	235
802766	1785	1804	52699	52718	TTTCTGAATCCCAGGATTTC	140	940
802767	1787	1806	52701	52720	CATTTCTGAATCCCAGGATT	97	941
802768	1788	1807	52702	52721	ACATTTCTGAATCCCAGGAT	60	942
802769	1790	1809	52704	52723	CCACATTTCTGAATCCCAGG	41	943
802770	1792	1811	52706	52725	ATCCACATTTCTGAATCCCA	57	944
802771	1794	1813	52708	52727	TAATCCACATTTCTGAATCC	119	945
802772	1806	1825	52720	52739	AGAAATTACTTTTAATCCAC	97	946
802773	1815	1834	52729	52748	TACAATAGAAGAAATTACTT	176	947
802774	1835	1854	52749	52768	TCTAATGCATCAGGAAAATG	145	948
802775	1844	1863	52758	52777	GATAACATCTCTAATGCATC	56	949
802776	1853	1872	52767	52786	CCTTCCAGGGATAACATCTC	125	950
802777	1862	1881	52776	52795	TCCATAGCACCTTCCAGGGA	73	951
802778	1868	1887	52782	52801	ACTGAATCCATAGCACCTTC	52	952
802779	1869	1888	52783	52802	CACTGAATCCATAGCACCTT	63	953
802780	1870	1889	52784	52803	GCACTGAATCCATAGCACCT	44	954
802781	1871	1890	52785	52804	AGCACTGAATCCATAGCACC	65	955
802782	1872	1891	52786	52805	AAGCACTGAATCCATAGCAC	70	956
802783	1874	1893	52788	52807	TGAAGCACTGAATCCATAGC	100	957
802784	1875	1894	52789	52808	GTGAAGCACTGAATCCATAG	53	958
802785	1876	1895	52790	52809	TGTGAAGCACTGAATCCATA	107	959
802786	1877	1896	52791	52810	GTGTGAAGCACTGAATCCAT	62	960
802787	1878	1897	52792	52811	TGTGTGAAGCACTGAATCCA	73	961
802788	1882	1901	52796	52815	GCAGTGTGTGAAGCACTGAA	100	962
802789	1891	1910	52805	52824	GATACATCTGCAGTGTGTGA	116	963
802790	1900	1919	52814	52833	GGTCATCTGGATACATCTGC	77	964
802791	1909	1928	N/A	N/A	GAATTTCTTGGTCATCTGGA	106	965
802792	1928	1947	52968	52987	AGACTTAAACCCAGACACTG	78	966
802793	1937	1956	52977	52996	TATCCTATAAGACTTAAACC	157	967
802794	1946	1965	52986	53005	GTAATCAAGTATCCTATAAG	105	968
802795	1972	1991	53012	53031	CAGTTCCTATGAACACATTC	76	969
802796	1981	2000	53021	53040	GCAGATGTCCAGTTCCTATG	79	970
802797	1990	2009	53030	53049	TTTTTGCCAGCAGATGTCCA	117	971
802798	1999	2018	53039	53058	AAACCAGAATTTTTGCCAGC	81	972
802799	2018	2037	53058	53077	TTAAATCGGTATAAGCTGGA	112	973
802800	2027	2046	53067	53086	GCAACATCCTTAAATCGGTA	78	974
802801	2036	2055	53076	53095	TGTATTTCAGCAACATCCTT	145	975
802802	2062	2081	N/A	N/A	CTAAGATTGTCTGAAATCCT	84	976
802803	2071	2090	56005	56024	TGAGGATTGCTAAGATTGTC	84	977
802804	2080	2099	56014	56033	CTGACAATTTGAGGATTGCT	58	978
802805	2106	2125	56040	56059	ATGCACCAGCAGCTTAGAAA	71	979
802806	2115	2134	56049	56068	AAATGAATGATGCACCAGCA	82	980
802807	2124	2143	56058	56077	TACTAAGTCAAATGAATGAT	109	981

802808	2151	2170	56085	56104	GATATTGGAAGACATTTGAT	143	982
802809	2160	2179	56094	56113	TTGTTCCATGATATTGGAAG	128	983
802810	2180	2199	N/A	N/A	TTTAGAAACTGTTGATCCTT	113	984
802811	2181	2200	N/A	N/A	GTTTAGAAACTGTTGATCCT	128	985
802812	2182	2201	N/A	N/A	GGTTTAGAAACTGTTGATCC	93	986
802813	2183	2202	N/A	N/A	AGGTTTAGAAACTGTTGATC	115	987
802814	2184	2203	N/A	N/A	GAGGTTTAGAAACTGTTGAT	118	988
802815	2186	2205	N/A	N/A	CAGAGGTTTAGAAACTGTTG	63	989
802816	2187	2206	N/A	N/A	ACAGAGGTTTAGAAACTGTT	84	990
802817	2188	2207	N/A	N/A	AACAGAGGTTTAGAAACTGT	119	991
802818	2189	2208	N/A	N/A	CAACAGAGGTTTAGAAACTG	99	992
802819	2190	2209	56198	56217	GCAACAGAGGTTTAGAAACT	94	993
802820	2194	2213	56202	56221	ACTTGCAACAGAGGTTTAGA	109	994
802821	2203	2222	56211	56230	TTGCAAAACACTTGCAACAG	120	995
802822	2212	2231	56220	56239	TAGCTACTTTTGCAAAACAC	88	996
802823	2238	2257	56246	56265	CATCACATTTTTTAAGTAAT	100	997
802824	2247	2266	56255	56274	TCTCTCTAGCATCACATTTT	80	998
802825	2256	2275	56264	56283	ATCACACGCTCTCTCTAGCA	57	999
802826	2282	2301	56290	56309	CATTCAACCATGATGCTGTT	79	72
802827	2291	2310	56299	56318	AGAAGCAAGCATTCAACCAT	103	1000
802828	2300	2319	56308	56327	GCTCCCAATAGAAGCAAGCA	108	1001
802829	2312	2331	56320	56339	TGATTGGCATCTGCTCCCAA	96	1002
802830	2313	2332	56321	56340	TTGATTGGCATCTGCTCCCA	67	1003
802831	2314	2333	56322	56341	CTTGATTGGCATCTGCTCCC	87	1004
802832	2315	2334	56323	56342	GCTTGATTGGCATCTGCTCC	54	1005
802833	2316	2335	56324	56343	TGCTTGATTGGCATCTGCTC	83	1006
802834	2318	2337	56326	56345	TTTGCTTGATTGGCATCTGC	82	125
802835	2319	2338	56327	56346	CTTTGCTTGATTGGCATCTG	80	1007
802836	2320	2339	56328	56347	CCTTTGCTTGATTGGCATCT	70	1008
802837	2321	2340	56329	56348	TCCTTTGCTTGATTGGCATC	94	1009
802838	2322	2341	56330	56349	CTCCTTTGCTTGATTGGCAT	75	1010
802839	2326	2345	56334	56353	ATCCCTCCTTTGCTTGATTG	124	1011
802840	2335	2354	56343	56362	TTAAAGAAGATCCCTCCTTT	186	1012
802841	2344	2363	56352	56371	CCTGACAAATTAAAGAAGAT	148	1013
802842	2357	2376	N/A	N/A	TCTTTCTCACATACCTGACA	69	1014

표 13

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
693433	2380	2399	62001	62020	GTTCCACCAATTTGGGACTG	41	126

[0600]

780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	30	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	22	235
802843	2358	2377	N/A	N/A	CTCTTTCTCACATACCTGAC	74	1015
802844	2360	2379	N/A	N/A	CTCTCTTTCTCACATACCTG	53	1016
802845	2365	2384	61986	62005	GACTGCTCTCTTTCTCACAT	34	1017
802846	2367	2386	61988	62007	GGGACTGCTCTCTTTCTCAC	39	1018
802847	2369	2388	61990	62009	TTGGGACTGCTCTCTTTCTC	53	1019
802848	2370	2389	61991	62010	TTTGGGACTGCTCTCTTTCT	59	1020
802849	2372	2391	61993	62012	AATTTGGGACTGCTCTCTTT	99	1021
802850	2373	2392	61994	62013	CAATTTGGGACTGCTCTCTT	83	1022
802851	2389	2408	62010	62029	TCAGTAAGAGTTCCACCAAT	65	1023
802852	2415	2434	62036	62055	TACATCTTGTTCACGAGATC	92	1024
802853	2460	2479	62081	62100	GATCTGGCTGTCACCTTTCC	65	1025
802854	2469	2488	62090	62109	CAAGCTGATGATCTGGCTGT	98	1026
802855	2478	2497	62099	62118	CCTTAAGAGCAAGCTGATGA	58	1027
802856	2487	2506	62108	62127	GGCCAGCCTCCTTAAGAGCA	74	1028
802857	2508	2527	62129	62148	GCTATTGTTGGCCACATCCA	44	1029
802858	2517	2536	62138	62157	AAGGCAAATGCTATTGTTGG	90	1030
802859	2526	2545	62147	62166	AAATCCTCCAAGGCAAATGC	92	1031
802860	2552	2571	62173	62192	CAAGAAGGTTCAACTTTTCC	87	1032
802861	2596	2615	62217	62236	GTTTCCTTAAATTAGAAGTC	169	1033
802862	2606	2625	N/A	N/A	ATATTTGTTTGTTTCCTTAA	81	1034
802863	2615	2634	N/A	N/A	GTAGATGCTATATTTGTTTG	82	1035
802864	2641	2660	65479	65498	GATATCTGATCACCATTCTT	78	1036
802865	2650	2669	65488	65507	TTTTCATCTGATATCTGATC	121	1037
802866	2659	2678	65497	65516	CCACAGCACTTTTCATCTGA	116	1038
802867	2668	2687	65506	65525	TTCCTTCTTCCACAGCACTT	115	1039
802868	2687	2706	65525	65544	CCATCGCTGCCTGAGGCTGT	69	1040
802869	2696	2715	65534	65553	GAAAAATTTCCATCGCTGCC	149	1041
802870	2705	2724	65543	65562	ACATCTTCAGAAAAATTTCC	86	1042
802871	2731	2750	65569	65588	AGGTCCATTCATCAAATTTA	77	1043
802872	2740	2759	65578	65597	CAGGAATAAAGGTCCATTCA	68	1044
802873	2749	2768	65587	65606	TAGAAGAGTCAGGAATAAAG	119	1045
802874	2761	2780	65599	65618	ACACACTGTCCATAGAAGAG	53	1046
802875	2763	2782	65601	65620	AAACACACTGTCCATAGAAG	102	1047
802876	2765	2784	65603	65622	GCAAACACACTGTCCATAGA	43	1048
802877	2767	2786	65605	65624	GAGCAAACACACTGTCCATA	42	1049
802878	2768	2787	65606	65625	TGAGCAAACACACTGTCCAT	70	1050
802879	2770	2789	65608	65627	TTTGAGCAAACACACTGTCC	124	1051
802880	2771	2790	65609	65628	CTTTGAGCAAACACACTGTC	141	1052
802881	2778	2797	65616	65635	GTCATCACTTTGAGCAAACA	90	1053
802882	2787	2806	65625	65644	ACTATCCAGGTCATCACTTT	121	1054
802883	2796	2815	N/A	N/A	ACTTCCTTCACTATCCAGGT	53	1055
802884	2819	2838	71662	71681	TTTTTCACAAGAAATGAGCC	96	1056
802885	2828	2847	71671	71690	TTAGATTTCTTTTTCACAAG	116	1057
802886	2837	2856	71680	71699	CTAATTGAATTAGATTTCTT	106	1058
802887	2863	2882	71706	71725	CGGCATCTCGGTAAAATTCT	48	1059
802888	2872	2891	71715	71734	GCTGTAATACGGCATCTCGG	27	1060

[0601]

802889	2907	2926	71750	71769	GGAATTGGAATGTCTTTGCA	76	1061
802890	2916	2935	N/A	N/A	GGGCCCCAAGGAATTGGAAT	102	1062
802891	2925	2944	N/A	N/A	ATCAAAAATGGGCCCCAAGG	87	1063
802892	2951	2970	72975	72994	CTTTTTCGCTTCAGTAAATC	79	1064
802893	2962	2981	72986	73005	ATAATATTTTTCTTTTTCGC	109	1065
802894	2971	2990	72995	73014	CATCTGAAGATAATATTTTT	141	1066
802895	2995	3014	N/A	N/A	GAAGTTTTGATGACCTGAGT	108	1067
802896	3004	3023	73540	73559	TATGGGATTGAAGTTTTGAT	56	1068
802897	3013	3032	73549	73568	AATGCCTCATATGGGATTGA	93	1069
802898	3022	3041	73558	73577	TGCTGTCTGAATGCCTCATA	60	1070
802899	3040	3059	73576	73595	CAGAAGCCAGAGAAGAAATG	135	1071
802900	3049	3068	73585	73604	ATTCTCTCTCAGAAGCCAGA	53	1072
802901	3058	3077	73594	73613	ATGTAATATATTCTCTCTCA	52	1073
802902	3084	3103	73620	73639	TAGTTCATTTGCTGAAAGGT	66	1074
802903	3093	3112	73629	73648	AATATCTCTTAGTTCATTTG	146	1075
802904	3102	3121	73638	73657	TAGGGCATCAATATCTCTTA	40	1076
802905	3111	3130	73647	73666	TTTCTGGCTTAGGGCATCAA	133	1077
802906	3129	3148	73665	73684	ATGAACACTTATACAGCATT	114	1078
802907	3138	3157	73674	73693	ATGCTCCAAATGAACACTTA	124	1079
802908	3147	3166	73683	73702	CTTTTCAAGATGCTCCAAAT	170	1080
802909	3173	3192	73709	73728	GTGAGTGCATTCTGGTGAAG	72	1081
802910	3192	3211	73728	73747	TAGCTGTTGTGGAAAGCTCG	114	1082
802911	3217	3236	N/A	N/A	GTGTCAAACTCTTCAGAGTT	34	1083
802912	3218	3237	76352	76371	TGTGTCAAACTCTTCAGAGT	60	1084
802913	3219	3238	76353	76372	ATGTGTCAAACTCTTCAGAG	63	1085
802914	3220	3239	76354	76373	AATGTGTCAAACTCTTCAGA	99	1086
802915	3226	3245	76360	76379	AGTCCAAATGTGTCAAACTC	23	1087
802916	3235	3254	76369	76388	TACTGTGCAAGTCCAAATGT	119	1088
802917	3244	3263	76378	76397	TAAATTTATTACTGTGCAAG	55	1089
802918	3265	3284	76399	76418	ACAAATAAGAAGGAAATGAT	196	1090

표 14

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	22	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	29	235
802919	3274	3293	76408	76427	TCATTTTCAACAAATAAGAA	110	1091
802920	3283	3302	76417	76436	CAATACAACTCATTTTCAAC	63	1092
802921	3309	3328	76443	76462	GTCATTTCGAGAGACATCAA	36	1093
802922	3318	3337	76452	76471	GGGTCCAATGTCATTTCGAG	38	1094

[0602]

802923	3327	3346	76461	76480	AACCACTGAGGGTCCAATGT	51	1095
802924	3353	3372	76487	76506	GTTGGACATTTCACTGTAGG	20	1096
802925	3362	3381	76496	76515	TGTTTCAGAGTTGGACATTT	77	1097
802926	3371	3390	76505	76524	AGGTTAAACTGTTTCAGAGT	36	1098
802927	3380	3399	76514	76533	TTATATGACAGGTTAAACTG	103	1099
802928	3398	3417	76532	76551	GGTACAAAAGACAGCTGGTT	34	1100
802929	3407	3426	76541	76560	AGGTTCTCAGGTACAAAAGA	47	1101
802930	3416	3435	76550	76569	ACATCAGTGAGGTTCTCAGG	37	1102
802931	3442	3461	76576	76595	AAATGAGCTGCTCCAGTTTC	75	1103
802932	3451	3470	N/A	N/A	TTCCTTCTAAAATGAGCTGC	53	1104
802933	3463	3482	N/A	N/A	CTGATATTTTATTTCCTTCT	69	1105
802934	3472	3491	77221	77240	AGCATATCCCTGATATTTTA	29	1106
802935	3495	3514	77244	77263	CAGTTCCTTCAGTCTCAAGG	32	1107
802936	3496	3515	77245	77264	TCAGTTCCTTCAGTCTCAAG	49	1108
802937	3497	3516	77246	77265	TTCAGTTCCTTCAGTCTCAA	80	1109
802938	3498	3517	77247	77266	CTTCAGTTCCTTCAGTCTCA	37	1110
802939	3499	3518	77248	77267	TCTTCAGTTCCTTCAGTCTC	56	1111
802940	3505	3524	77254	77273	TTAAAATCTTCAGTTCCTTC	59	1112
802941	3514	3533	77263	77282	TACTAAGGTTTAAAATCTTC	105	1113
802942	3523	3542	77272	77291	TGTGGTTCTTACTAAGGTTT	38	1114
802943	3547	3566	77296	77315	GAAAGTTCTCTGATAGGGAT	59	1115
802944	3556	3575	77305	77324	AAGCCTCAAGAAAGTTCTCT	59	1116
802945	3565	3584	77314	77333	CTTTAGGACAAGCCTCAAGA	65	132
802946	3591	3610	77340	77359	ATTCATTCTGGCACTGAAAC	136	1117
802947	3600	3619	N/A	N/A	AGCAAGAAAATTCATTCTGG	75	1118
802948	3609	3628	N/A	N/A	AGGCATAGCAGCAAGAAAAT	57	1119
802949	3635	3654	80915	80934	AGGATTGTCATAGAAGGAGG	19	1120
802950	3644	3663	80924	80943	GATAATTTTAGGATTGTCAT	58	1121
802951	3654	3673	80934	80953	TTTGTTCTGAGATAATTTTA	32	1122
802952	3679	3698	80959	80978	AAATTGCTTCTGGAATACAG	75	1123
802953	3688	3707	80968	80987	GAAGATTTAAAATTGCTTCT	115	1124
802954	3697	3716	N/A	N/A	GCAAGTGTGGAAGATTTAAA	50	1125
802955	3709	3728	N/A	N/A	TATCTAAAGACCGCAAGTGT	51	1126
802956	3710	3729	N/A	N/A	ATATCTAAAGACCGCAAGTG	62	1127
802957	3711	3730	N/A	N/A	CATATCTAAAGACCGCAAGT	63	1128
802958	3712	3731	82057	82076	TCATATCTAAAGACCGCAAG	71	1129
802959	3713	3732	82058	82077	CTCATATCTAAAGACCGCAA	47	1130
802960	3715	3734	82060	82079	TGCTCATATCTAAAGACCGC	35	1131
802961	3716	3735	82061	82080	CTGCTCATATCTAAAGACCG	43	1132
802962	3717	3736	82062	82081	GCTGCTCATATCTAAAGACC	28	1133
802963	3718	3737	82063	82082	TGCTGCTCATATCTAAAGAC	64	1134
802964	3719	3738	82064	82083	TTGCTGCTCATATCTAAAGA	79	1135
802965	3723	3742	82068	82087	ATCATTGCTGCTCATATCTA	82	1136
802966	3732	3751	82077	82096	GTACTGAATATCATTGCTGC	31	1137
802967	3741	3760	82086	82105	ACCTGGTAGGTACTGAATAT	50	1138
802968	3767	3786	82112	82131	AAGTTCAAAGATTTCCAGTG	50	1139
802969	3776	3795	82121	82140	AGTTCCCTTAAGTTCAAAGA	78	1140
802970	3785	3804	82130	82149	CTAAATAAGAGTTCCCTTAA	75	1141

[0603]

802971	3811	3830	82156	82175	AGTCCAAGATGCTGATCTGA	49	1142
802972	3820	3839	82165	82184	TTTCACTCAAGTCCAAGATG	52	1143
802973	3829	3848	82174	82193	AATATGCTTTTTCACTCAAG	64	1144
802974	3855	3874	82200	82219	ATGCAGTTTCTCTACTCTAG	31	1145
802975	3864	3883	82209	82228	GTGAGAAAGATGCAGTTTCT	47	1146
802976	3873	3892	82218	82237	CAGTTTATTGTGAGAAAGAT	89	1147
802977	3882	3901	N/A	N/A	AATCTCTTTCAGTTTATTGT	65	1148
802978	3900	3919	83895	83914	ACAGCCAATCTCAGGAGGAA	56	1149
802979	3909	3928	83904	83923	ATTTTCAAGACAGCCAATCT	72	1150
802980	3918	3937	83913	83932	AGATGTCAGATTTTCAAGAC	141	1151
802981	3944	3963	83939	83958	AGTTCCAAGTTGTAACTGAC	59	57
802982	3953	3972	83948	83967	AAGGATCTTAGTTCCAAGTT	89	1152
802983	3962	3981	83957	83976	TCATTGGGAAAGGATCTTAG	107	1153
802984	3988	4007	83983	84002	CCCATATTTTGCTTAATTTC	54	1154
802985	3997	4016	83992	84011	AAGGAAGATCCCATATTTTG	72	1155
802986	4006	4025	84001	84020	GTTCATCCAAAGGAAGATCC	40	1156
802987	4033	4052	84028	84047	TATGTTTAAAATCAAAGTTA	128	1157
802988	4042	4061	84037	84056	TACATCCTATATGTTTAAAA	101	1158
802989	4060	4079	84055	84074	TTATGATGTCTTTGGCTTTA	41	1159
802990	4061	4080	84056	84075	CTTATGATGTCTTTGGCTTT	53	1160
802991	4063	4082	84058	84077	ACCTTATGATGTCTTTGGCT	36	1161
802992	4065	4084	N/A	N/A	AAACCTTATGATGTCTTTGG	41	1162
802993	4068	4087	N/A	N/A	AAGAAACCTTATGATGTCTT	80	1163
802994	4078	4097	N/A	N/A	ATCGCTGTTGAAGAAACCTT	38	1164
802995	4087	4106	86582	86601	CCTTTTTTAATCGCTGTTGA	69	1165

표 15

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	31	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	51	235
802996	4096	4115	86591	86610	AAGGCACAGCCTTTTTTAAT	88	1166
802997	4106	4125	86601	86620	ATTCGGTTATAAGGCACAGC	39	1167
802998	4107	4126	86602	86621	CATTCGGTTATAAGGCACAG	54	1168
802999	4108	4127	86603	86622	TCATTCGGTTATAAGGCACA	51	1169
803000	4109	4128	86604	86623	TTCATTCGGTTATAAGGCAC	34	1170
803001	4110	4129	86605	86624	TTTCATTCGGTTATAAGGCA	47	1171
803002	4112	4131	86607	86626	AGTTTCATTCGGTTATAAGG	57	1172
803003	4113	4132	86608	86627	AAGTTTCATTCGGTTATAAG	72	1173
803004	4114	4133	86609	86628	TAAGTTTCATTCGGTTATAA	89	1174

[0604]

803005	4115	4134	86610	86629	ATAAGTTTCATTCGGTTATA	44	1175
803006	4116	4135	86611	86630	CATAAGTTTCATTCGGTTAT	45	1176
803007	4120	4139	86615	86634	CAATCATAAGTTTCATTCGG	51	1177
803008	4129	4148	86624	86643	TATTTCCCACAATCATAAGT	98	1178
803009	4138	4157	86633	86652	CACTCCCAGTATTTCCCACA	69	1179
803010	4164	4183	86659	86678	TAATTGCTGCAATAAGGTGG	51	1180
803011	4173	4192	86668	86687	GGTTTTCATTAATTGCTGCA	40	1181
803012	4184	4203	86679	86698	TCTGATTTCTTGGTTTTCAT	58	1182
803013	4208	4227	86703	86722	ACTGTGGCACTTTGCATTCC	80	1183
803014	4217	4236	86712	86731	TCTATGCCAACTGTGGCACT	79	1184
803015	4226	4245	86721	86740	TCTTTCACATCTATGCCAAC	79	1185
803016	4252	4271	86747	86766	TTTTGTCTCTTATTTGGATA	44	1186
803017	4267	4286	86762	86781	CGAGATCTCTCTTTCTTTTG	56	1187
803018	4276	4295	86771	86790	CATTTAGGACGAGATCTCTC	92	1188
803019	4296	4315	N/A	N/A	ACGACCTGCAAAATCCCACA	65	1189
803020	4305	4324	N/A	N/A	GAATTCCTCACGACCTGCAA	90	83
803021	4314	4333	87218	87237	AGTACTATAGAATTCCTCAC	35	1190
803022	4359	4378	87263	87282	ATAGACAGCAAGGTACAATG	101	1191
803023	4368	4387	87272	87291	GCTGAGGTCATAGACAGCAA	101	1192
803024	4377	4396	87281	87300	CTGTCCCTTGCTGAGGTCAT	89	1193
803025	4403	4422	87307	87326	CAAGGCTTCATGGCATCAAC	85	1194
803026	4412	4431	87316	87335	TTGAAGAGCCAAGGCTTCAT	96	1195
803027	4421	4440	N/A	N/A	GCCTTTATATTGAAGAGCCA	62	1196
803028	4456	4475	88557	88576	TGCCAACGAGAATCACAGGG	45	1197
803029	4465	4484	88566	88585	CCAAATGTGTGCCAACGAGA	70	1198
803030	4474	4493	88575	88594	CAGAAACATCCAAATGTGTG	69	1199
803031	4505	4524	88606	88625	TTACTCATGCAGGCTTTGCG	44	1200
803032	4514	4533	88615	88634	TTGGTGATTTTACTCATGCA	43	1201
803033	4536	4555	88637	88656	CCCTCGCTTATTCAGGAGTT	98	1202
803034	4545	4564	88646	88665	GGCAGGGAACCCTCGCTTAT	61	1203
803035	4580	4599	88681	88700	TCCTCGGTGGCATTCACAAA	60	42
803036	4589	4608	88690	88709	GCATCAGATTCCTCGGTGGC	39	1204
803037	4598	4617	88699	88718	TTTGCCAAAGCATCAGATTC	67	1205
803038	4639	4658	N/A	N/A	TCTTGAAATTAAGGCTCTCG	91	1206
803039	4648	4667	N/A	N/A	GATCTCGGATCTTGAAATTA	125	1207
803040	4668	4687	92091	92110	CAGCTGTCCAACAACAAGCT	81	1208
803041	4677	4696	92100	92119	GTCTGGAATCAGCTGTCCAA	55	1209
803042	4686	4705	92109	92128	TACATAGCAGTCTGGAATCA	75	1210
803043	4712	4731	92135	92154	TCCGATAAAATGATTTTTTC	60	1211
803044	4721	4740	92144	92163	TTTTTACGCTCCGATAAAAT	132	1212
803045	4730	4749	92153	92172	ATTGGCACATTTTTACGCTC	24	1213
803046	4756	4775	92179	92198	GTTTCCGGTCAATTACGGGA	21	1214
803047	4775	4794	92198	92217	CTCACTAGTTGTAATAATCG	63	1215
803048	4800	4819	92223	92242	TTCATCTAACTGCAGCTGAT	59	1216
803049	4810	4829	92233	92252	GAAGCTCATTTTCATCTAAC	49	1217
803050	4844	4863	N/A	N/A	ACTCCTGATTCATTTAGAAA	88	1218
803051	4853	4872	N/A	N/A	TGAAGAAGGACTCCTGATTC	99	1219
803052	4862	4881	93323	93342	TCTTGAAAATGAAGAAGGAC	100	1220

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803053	4871	4890	93332	93351	AGTGCTGGGTCTTGAAAATG	55	1221
803054	4892	4911	93353	93372	AAGTACAAGTCACTTAACTG	38	1222
803055	4938	4957	N/A	N/A	TGTCAAAATCTGTGCCATGA	70	1223
803056	4947	4966	98095	98114	CACTTTCACTGTCAAAATCT	76	1224
803057	4956	4975	98104	98123	ACAACCTTCCACTTTCACTG	65	1225
803058	4982	5001	98130	98149	GAAATAATGCCCTTAGGGTG	98	1226
803059	4991	5010	98139	98158	TCTCTACGCGAAATAATGCC	58	1227
803060	5000	5019	98148	98167	TTTTCCACATCTCTACGCGA	49	1228
803061	5009	5028	98157	98176	GAAAGAAATTTTTCCACATC	65	1229
803062	5028	5047	98176	98195	TGGAAATTTCCTTTTTTTTG	81	1230
803063	5038	5057	98186	98205	TGTAGTTCTTTGGAAATTTC	45	1231
803064	5047	5066	98195	98214	ACTGTGACATGTAGTTCTTT	29	1232
803065	5072	5091	98220	98239	TGGAATTTTTCTAGGAGCTT	23	1233
803066	5082	5101	98230	98249	CAAAGCAATCTGGAATTTTT	104	1234
803067	5091	5110	98239	98258	TCCTATTGGCAAAGCAATCT	79	1235
803068	5100	5119	98248	98267	ATATTCTTCTCCTATTGGCA	84	1236
803069	5118	5137	N/A	N/A	ACTGCTTGGAACCAGCAAAT	72	1237
803070	5127	5146	N/A	N/A	GTCAGACAAACTGCTTGGAA	84	1238
803071	5136	5155	99142	99161	AGGCCTGTGGTCAGACAAAC	87	1239
803072	5145	5164	99151	99170	CTCTATCACAGGCCTGTGGT	73	1240

표 16

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	11	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	26	235
803073	5178	5197	99184	99203	GATGATAATTTCAGAGTTCT	49	1241
803074	5187	5206	99193	99212	ATATAGTCGGATGATAATTT	53	1242
803075	5196	5215	99202	99221	AGGCATTTCATATAGTCGGA	11	1243
803076	5206	5225	99212	99231	TTGGAAAATAAGGCATTTCA	48	1244
803077	5227	5246	99233	99252	TTAATCTTGACCAAAATCCC	76	1245
803078	5236	5255	99242	99261	ATCGATTGATTAATCTTGAC	48	1246
803079	5245	5264	99251	99270	TCTCAAGTAATCGATTGATT	34	1247
803080	5270	5289	99276	99295	CTCCCTGAAAGCATGTAAGG	64	1248
803081	5294	5313	100146	100165	CTGTTTGGGCGAAGTGCTCG	45	1249
803082	5300	5319	100152	100171	TACATTCTGTTTGGGCGAAG	52	1250
803083	5301	5320	100153	100172	ATACATTCTGTTTGGGCGAA	40	1251
803084	5302	5321	100154	100173	AATACATTCTGTTTGGGCGA	33	1252
803085	5303	5322	100155	100174	CAATACATTCTGTTTGGGCG	39	1253
803086	5304	5323	100156	100175	CCAATACATTCTGTTTGGGC	48	1254

[0606]

803087	5306	5325	100158	100177	CGCCAATACATTCTGTTTGG	36	1255
803088	5307	5326	100159	100178	TCGCCAATACATTCTGTTTG	44	1256
803089	5308	5327	100160	100179	GTCGCCAATACATTCTGTTT	57	1257
803090	5309	5328	100161	100180	TGTCGCCAATACATTCTGTT	55	1258
803091	5310	5329	100162	100181	TTGTCGCCAATACATTCTGT	62	1259
803092	5314	5333	100166	100185	TGCCTTGTCGCCAATACATT	46	1260
803093	5323	5342	100175	100194	TTAAGTAAATGCCTTGTCGC	61	1261
803094	5332	5351	100184	100203	GAGACCAATTTAAGTAAATG	63	1262
803095	5358	5377	100210	100229	AGATCCTACCAGACAATAAG	83	1263
803096	5367	5386	100219	100238	TAAGACTTCAGATCCTACCA	49	1264
803097	5376	5395	100228	100247	ATGATTGTCTAAGACTTCAG	38	1265
803098	5385	5404	100237	100256	ACTCTCTGGATGATTGTCTA	36	1266
803099	5405	5424	100257	100276	GGAACTGTAATTTTTAAGAA	98	1267
803100	5414	5433	100266	100285	CTACAAGAAGGAACTGTAAT	98	1268
803101	5423	5442	N/A	N/A	CAGCCTTTTCTACAAGAAGG	40	1269
803102	5449	5468	100438	100457	GGTCCACAACTTGGCCCAAA	28	1270
803103	5458	5477	100447	100466	AATCAATGTGGTCCACAACT	70	1271
803104	5467	5486	100456	100475	CCATGAGAGAATCAATGTGG	35	1272
803105	5476	5495	100465	100484	ACCATTCTTCCATGAGAGAA	36	1273
803106	5497	5516	100486	100505	CAATCTCCAGCAACCCAGGA	69	1274
803107	5507	5526	100496	100515	CCACAAATATCAATCTCCAG	45	1275
803108	5516	5535	100505	100524	TCTCCTTCACCACAAATATC	46	1276
803109	5533	5552	100522	100541	ATTTCTTCAACAGAGTTTCT	103	1277
803110	5534	5553	100523	100542	CATTTCTTCAACAGAGTTTC	64	1278
803111	5536	5555	100525	100544	CCCATTTCTTCAACAGAGTT	36	1279
803112	5538	5557	100527	100546	TGCCCATTTCTTCAACAGAG	22	1280
803113	5540	5559	100529	100548	AATGCCCATTTCTTCAACAG	53	1281
803114	5541	5560	100530	100549	TAATGCCCATTTCTTCAACA	67	1282
803115	5551	5570	100540	100559	TAAAACTATATAATGCCCAT	49	1283
803116	5560	5579	100549	100568	CACCATCATTAAAACTATAT	72	1284
803117	5586	5605	100575	100594	ATCAAGTAAGATTTTTTGAT	84	1285
803118	5595	5614	100584	100603	CATCAAGTCATCAAGTAAGA	70	1286
803119	5604	5623	100593	100612	TGCTTTCTTCATCAAGTCAT	80	1287
803120	5631	5650	101269	101288	TGGATTTACTAAGAGATCTC	36	1288
803121	5640	5659	101278	101297	TGGTTGATCTGGATTTACTA	49	1289
803122	5649	5668	101287	101306	GGTGAGCCTTGGTTGATCTG	28	1290
803123	5689	5708	101327	101346	CAGCCAAAATCAAGTCAGGG	29	1291
803124	5698	5717	101336	101355	TAGGCAGGTCAGCCAAAATC	47	1292
803125	5721	5740	101359	101378	ATCATTATTCAACATAATAT	78	1293
803126	5730	5749	101368	101387	TTCCAACTCATCATTATTCA	37	1294
803127	5739	5758	101377	101396	TTGTTCAAATTCCAACTCAT	79	1295
803128	5763	5782	N/A	N/A	ATCACCTAGGAGAAACTCTG	52	1296
803129	5772	5791	N/A	N/A	AAAACTGCCATCACCTAGGA	60	1297
803130	5781	5800	106472	106491	AACTGATCCAAAACTGCCAT	51	1298
803131	5807	5826	106498	106517	TCTTCTCCTTCATAGGCTGC	55	1299
803132	5816	5835	106507	106526	ACAGCCACTTCTTCTCCTTC	80	1300
803133	5825	5844	106516	106535	AAAATCTTCACAGCCACTTC	102	92
803134	5851	5870	106542	106561	ACAGCCTGAGTGATGTATGT	32*	1301

[0607]

803135	5860	5879	106551	106570	CTTGTCTTAACAGCCTGAGT	28*	1302
803136	5869	5888	N/A	N/A	CCACAAGCTCTTGTCTTAAC	34*	1303
803137	5909	5928	113106	113125	AGCAAAGATATCAAACTGGG	51*	1304
803138	5918	5937	113115	113134	CCAGCTGCCAGCAAAGATAT	44*	1305
803139	5927	5946	113124	113143	GGACGAATCCCAGCTGCCAG	42*	1306
803140	5955	5974	113152	113171	GGAGGCTAACTCCATCACCA	35	1307
803141	5964	5983	113161	113180	GGAACCCTTGGAGGCTAACT	89	1308
803142	5973	5992	113170	113189	GCGATCCAAGGAACCCTTGG	91	1309
803143	5999	6018	113196	113215	AGGCTGGCTTTGTCCTGCTG	110	1310
803144	6008	6027	113205	113224	GTTCTAGTGAGGCTGGCTTT	75	1311
803145	6017	6036	113214	113233	TGCTGTAGGGTTCTAGTGAG	93	1312
803146	6052	6071	N/A	N/A	ATCTCAAACCATCAGCTACG	76	1313
803147	6061	6080	N/A	N/A	AGTGGAGGTATCTCAAACCA	85	1314
803148	6087	6106	118420	118439	CAGGTCTCGGTATATAATCA	69	1315
803149	6111	6130	118444	118463	GAAAAGCAGCACATTGTGGG	47	1316

표 17

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	12	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	24	235
803150	6131	6150	118464	118483	GCAGCATTGGGATACAGTGT	53	1317
803151	6140	6159	118473	118492	GCAATGATGGCAGCATTGGG	59	1318
803152	6149	6168	118482	118501	GCAATCTTTGCAATGATGGC	56	159
803153	6189	6208	118522	118541	TATCCCCATTCTACAGCAGT	81	1319
803154	6198	6217	118531	118550	TGATGTTTTTATCCCCATTC	98	1320
803155	6220	6239	N/A	N/A	CACGAAACCCTGGTGTGCCC	58	1321
803156	6229	6248	124860	124879	CTTCAGGTGCACGAAACCCT	101	1322
803157	6238	6257	124869	124888	CTCTGGCAACTTCAGGTGCA	65	1323
803158	6264	6283	124895	124914	AGCCTGTTGGTTATAAATGA	64	1324
803159	6273	6292	124904	124923	ATAAACATCAGCCTGTTGGT	83	1325
803160	6282	6301	124913	124932	ACCAAATGAATAAACATCAG	60	1326
803161	6308	6327	124939	124958	GTTGTCAAAATGTCATAGAG	57	1327
803162	6317	6336	124948	124967	CTACCTCCAGTTGTCAAAAT	72	1328
803163	6326	6345	124957	124976	TCTACTATTCTACCTCCAGT	57	1329
803164	6335	6354	124966	124985	TTCAAACCCTCTACTATTCT	85	1330
803165	6354	6373	124985	125004	ATCAAACTCATTTGGAAACT	71	1331
803166	6363	6382	124994	125013	TTCTAATTCATCAAACTCAT	90	1332
803167	6372	6391	125003	125022	TCCTTGTATTTCTAATTCAT	93	1333
803168	6398	6417	N/A	N/A	TATTCTTTAACTGGATCAGG	81	1334

[0608]

803169	6407	6426	126523	126542	GCACAACCATATTCTTTAAC	70	1335
803170	6442	6461	126558	126577	ACTGTTTAATTAATTTCTCA	60	1336
803171	6451	6470	126567	126586	CTTTCAAACACTGTTTAATT	68	1337
803172	6460	6479	126576	126595	GAGGATTTTCTTTCAAACAC	39	1338
803173	6486	6505	N/A	N/A	GACCTGGGCAGAAGTAGGCC	62	1339
803174	6495	6514	N/A	N/A	AATGTCAAAGACCTGGGCAG	94	1340
803175	6504	6523	129649	129668	TGAATTCAAAATGTCAAAGA	113	1341
803176	6548	6567	129693	129712	TTTTTAGGTAATAAAATGCG	112	1342
803177	6577	6596	129722	129741	GTGTAGCAACCATGCATTCA	32	1343
803178	6586	6605	129731	129750	TGTTGTGATGTGTAGCAACC	54	162
803179	6595	6614	129740	129759	CATTCCTGCTGTTGTGATGT	66	1344
803180	6607	6626	129752	129771	GCCAAATGCTTGCATTCCTG	42	1345
803181	6608	6627	129753	129772	AGCCAAATGCTTGCATTCCT	38	1346
803182	6609	6628	129754	129773	CAGCCAAATGCTTGCATTCC	64	1347
803183	6610	6629	129755	129774	CCAGCCAAATGCTTGCATTC	53	1348
803184	6611	6630	129756	129775	CCCAGCCAAATGCTTGCATT	59	1349
803185	6613	6632	129758	129777	AGCCCAGCCAAATGCTTGCA	43	163
803186	6614	6633	129759	129778	CAGCCCAGCCAAATGCTTGC	73	1350
803187	6615	6634	129760	129779	ACAGCCCAGCCAAATGCTTG	97	1351
803188	6616	6635	129761	129780	CACAGCCCAGCCAAATGCTT	90	1352
803189	6617	6636	129762	129781	CCACAGCCCAGCCAAATGCT	104	1353
803190	6621	6640	129766	129785	GTGCCCACAGCCCAGCCAAA	60	1354
803191	6630	6649	129775	129794	TCTGTCGGTGTGCCCACAGC	77	1355
803192	6639	6658	129784	129803	GAGCTGTCCTCTGTCGGTGT	71	1356
803193	6665	6684	129810	129829	CCTTCAGTATTTAAGTCAAG	75	1357
803194	6674	6693	129819	129838	GAAGTGTATCCTTCAGTATT	76	1358
803195	6683	6702	N/A	N/A	ACTTCCTCAGAAGTGTATCC	89	1359
803196	6709	6728	132419	132438	CTAAGCACAATATTCTACTA	65	1360
803197	6718	6737	132428	132447	GCACCAAGGCTAAGCACAAT	54	1361
803198	6727	6746	132437	132456	CAGGAAGATGCACCAAGGCT	53	1362
803199	6753	6772	132463	132482	AGACACAATCCAGCTTTCCT	113	1363
803200	6762	6781	132472	132491	CTGTGTCCCAGACACAATCC	91	1364
803201	6771	6790	132481	132500	AGTACCAGACTGTGTCCCAG	74	1365
803202	6797	6816	132507	132526	CCATCTTCGGTATTGATGAC	57	1366
803203	6806	6825	132516	132535	CTCTTTTTCCCATCTTCGGT	61	1367
803204	6815	6834	132525	132544	AGGGTATGTCTCTTTTTCCC	42	1368
803205	6841	6860	132551	132570	AAGTGACAGAATCAGTCATC	71	52
803206	6850	6869	132560	132579	AATACAAACAAGTGACAGAA	98	1369
803207	6864	6883	132574	132593	GGAAAAGGAATTGCAATACA	76	1370
803208	6902	6921	134234	134253	GTTCCAACCAAAAGAAAATT	86	1371
803209	6911	6930	134243	134262	CCATCAGCGGTTCCAACCAA	55	1372
803210	6929	6948	134261	134280	TCAAAAATTGCTAACTTGCC	111	1373
803211	6938	6957	134270	134289	GTCTTATCTTCAAAAATTGC	92	1374
803212	6947	6966	N/A	N/A	AGCTTAACAGTCTTATCTTC	94	1375
803213	6973	6992	137377	137396	GTATCTTCAAAGGAGCAGCT	72	1376
803214	6983	7002	137387	137406	CCTATATTTAGTATCTTCAA	54	1377
803215	6992	7011	137396	137415	CTGACATTTCCTATATTTAG	73	1378
803216	7017	7036	137421	137440	TTCACTCAAACACATCAATG	68	1379

[0609]

803217	7026	7045	137430	137449	ATTTGTGGATTCACTCAAAC	72	1380
803218	7035	7054	137439	137458	TTCCGTTGAATTTGTGGATT	85	1381
803219	7061	7080	137465	137484	CCACATCCTCCCCACATTAC	62	1382
803220	7070	7089	137474	137493	ATCTTTGTGCCACATCCTCC	77	1383
803221	7087	7106	137491	137510	CATTAGAAAAGGAGAAAATC	85	1384
803222	7105	7124	137509	137528	GTTTCTGAATGGTGAAATCA	76	1385
803223	7114	7133	137518	137537	TCTCAATGAGTTTCTGAATG	74	1386
803224	7123	7142	137527	137546	TTGTTCTTGTCTCAATGAGT	100	1387
803225	7132	7151	137536	137555	ACAGTTGGCTTGTTCTTGTC	104	1388
803226	7150	7169	141511	141530	TGAAAGCTGCATAAGAAAAC	116	1389

표 18

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	25	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	20	235
803227	7159	7178	141520	141539	TGGAATCACTGAAAGCTGCA	65	1390
803228	7168	7187	141529	141548	TTATGATGTTGGAATCACTG	60	1391
803229	7194	7213	141555	141574	ATAGAGAGCAGTGTCTACCA	66	1392
803230	7203	7222	141564	141583	CTTAGCAATATAGAGAGCAG	97	1393
803231	7212	7231	141573	141592	GCTATTTTGCTTAGCAATAT	46	1394
803232	7238	7257	141599	141618	TTCTTATCCCACACTTCCAC	89	1395
803233	7248	7267	141609	141628	TTTTTCAGTTTTCTTATCCC	75	1396
803234	7257	7276	141618	141637	TCCACAGAGTTTTTCAGTTT	64	1397
803235	7282	7301	141643	141662	TTAAAAAGTGCACGCAGTCT	108	1398
803236	7291	7310	N/A	N/A	TTACCTCCCTTAAAAAGTGC	95	1399
803237	7300	7319	N/A	N/A	CTTTTACCATTACCTCCCTT	80	1400
803238	7309	7328	142957	142976	CCTTGTTTTCTTTTACCATT	65	1401
803239	7339	7358	142987	143006	TCCCAGAATAAGACATTTTG	68	1402
803240	7348	7367	142996	143015	TTTTCACTCTCCCAGAATAA	62	1403
803241	7371	7390	143019	143038	AGTGTTCTTCTGAAGGCAGA	60	1404
803242	7380	7399	143028	143047	CCAAAGAGCAGTGTTCTTCT	86	1405
803243	7389	7408	143037	143056	AGTTCCTATCCAAAGAGCAG	87	1406
803244	7415	7434	143063	143082	TCCAGGAGTAAAATATGGCC	51	1407
803245	7424	7443	143072	143091	GTTGAAAGATCCAGGAGTAA	106	1408
803246	7433	7452	143081	143100	AGTCGACGAGTTGAAAGATC	106	1409
803247	7466	7485	143114	143133	ACCGAATTACAAAAGTTGTA	71	1410
803248	7475	7494	143123	143142	ATGACTCTGACCGAATTACA	82	1411
803249	7484	7503	143132	143151	GCTGTCATCATGACTCTGAC	65	1412
803250	7510	7529	145113	145132	TGACATTTTTAAGGCTTCCT	58	1413

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803251	7522	7541	145125	145144	CCAATACCAGCATGACATTT	75	1414
803252	7531	7550	145134	145153	GGTTGTAGCCCAATACCAGC	74	1415
803253	7554	7573	145157	145176	TTGTGTACCTTCAGTATTTT	61	1416
803254	7564	7583	145167	145186	CTTTCTGCTTTTGTGTACCT	92	1417
803255	7573	7592	N/A	N/A	ATTGTATCTCTTTCTGCTTT	104	1418
803256	7598	7617	145767	145786	TTGATGTCCCAAACGGTCAA	49	1419
803257	7607	7626	145776	145795	TGTGGAAGATTGATGTCCCA	96	1420
803258	7616	7635	145785	145804	TGCACTTCATGTGGAAGATT	74	1421
803259	7625	7644	145794	145813	TCTAAATTTTGCACTTCATG	71	1422
803260	7645	7664	145814	145833	TTCTCACTTCAATGTGTTTT	48	1423
803261	7654	7673	145823	145842	CTAATTCTTTTCTCACTTCA	93	1424
803262	7666	7685	145835	145854	TCATTTTTTCAGCTAATTCT	95	1425
803263	7697	7716	145866	145885	CTATTTCTCTCTTACTCAAC	77	1426
803264	7706	7725	145875	145894	AGACAATTCCTATTTCTCTC	45	1427
803265	7717	7736	145886	145905	TTCCTATCCAAAGACAATTC	83	1428
803266	7741	7760	145910	145929	TATTTACAAGAGGAGAGAAT	75	1429
803267	7771	7790	145940	145959	CCCTTTCCATGTGAACATTT	65	1430
803268	7772	7791	145941	145960	ACCCTTTCCATGTGAACATT	49	1431
803269	7773	7792	145942	145961	TACCCTTTCCATGTGAACAT	49	1432
803270	7774	7793	145943	145962	GTACCCTTTCCATGTGAACA	41	1433
803271	7775	7794	145944	145963	AGTACCCTTTCCATGTGAAC	54	1434
803272	7777	7796	145946	145965	TGAGTACCCTTTCCATGTGA	43	1435
803273	7778	7797	145947	145966	GTGAGTACCCTTTCCATGTG	44	1436
803274	7779	7798	145948	145967	TGTGAGTACCCTTTCCATGT	66	1437
803275	7780	7799	145949	145968	ATGTGAGTACCCTTTCCATG	37	1438
803276	7781	7800	145950	145969	AATGTGAGTACCCTTTCCAT	57	1439
803277	7785	7804	145954	145973	AAAAAATGTGAGTACCCTTT	68	1440
803278	7794	7813	145963	145982	AGCTATTTCAAAAAATGTGA	89	1441
803279	7803	7822	145972	145991	ATACACACGAGCTATTTCAA	76	1442
803280	7812	7831	145981	146000	CATTCCTTCATACACACGAG	57	1443
803281	7850	7869	146019	146038	GTAAGTATTTTTACATATAT	69	1444
803282	7876	7895	146045	146064	TAGTTCTTTAAAATACACAT	58	1445
803283	7888	7907	146057	146076	TTGTGTTTTAAATAGTTCTT	56	1446
803284	7897	7916	146066	146085	AATATAACATTGTGTTTTAA	95	1447
803285	7921	7940	146090	146109	CGAAAGTAACTGGTATTTAT	40	1448
803286	7930	7949	146099	146118	ATTAATGAACGAAAGTAACT	125	1449
803287	7939	7958	146108	146127	TTTTCATTAATTAATGAACG	99	1450
803288	7948	7967	146117	146136	ACAGATTTATTTTCATTAAT	82	1451
803289	7969	7988	146138	146157	AGTACTTAAATTAGGTACTT	126	1452
803290	7978	7997	146147	146166	TTTAGTATGAGTACTTAAAT	102	1453
803291	7987	8006	146156	146175	CTTATAAATTTTAGTATGAG	98	1454
803292	8019	8038	146188	146207	CATTACAGACAAGAAAACAA	109	1455
803293	8028	8047	146197	146216	GTTTACCTCCATTACAGACA	61	1456
803294	8037	8056	146206	146225	TAAAATAAAGTTTACCTCCA	59	1457
803295	8061	8080	146230	146249	TAGTCCTGTCTTAAGCACAG	74	1458
803296	8070	8089	146239	146258	GACAAGCAATAGTCCTGTCT	66	1459
803297	8079	8098	146248	146267	AGAAAAATCGACAAGCAATA	89	1460
803298	8105	8124	146274	146293	ATTTTCATTATACCGTGCAG	55	1461

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803299	8116	8135	146285	146304	ACTGTCTTAATATTTTCATT	53	1462
803300	8125	8144	146294	146313	ACATGGGAAACTGTCTTAAT	56	1463
803301	8149	8168	146318	146337	ATGCAATCTAAGAAGGAATA	67	1464
803302	8158	8177	146327	146346	TGCATTTCGATGCAATCTAA	36	1465
803303	8167	8186	146336	146355	ATATGATAGTGCATTTCGAT	69	1466

표 19

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	27	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	12	235
803304	8176	8195	146345	146364	TACAAGCATATATGATAGTG	83	1467
803305	8207	8226	146376	146395	GACTTTATTAGTGCAAATTC	54	1468
803306	8208	8227	146377	146396	GGACTTTATTAGTGCAAATT	45	1469
803307	8209	8228	146378	146397	AGGACTTTATTAGTGCAAAT	54	1470
803308	8210	8229	146379	146398	AAGGACTTTATTAGTGCAAA	56	1471
803309	8212	8231	146381	146400	CAAAGGACTTTATTAGTGCA	59	1472
803310	8213	8232	146382	146401	ACAAAGGACTTTATTAGTGC	58	1473
803311	8214	8233	146383	146402	AACAAAGGACTTTATTAGTG	63	1474
803312	8215	8234	146384	146403	CAACAAAGGACTTTATTAGT	101	1475
803313	8240	8259	146409	146428	ACAGCAACAAAGAGAATTCA	88	1476
803314	8252	8271	146421	146440	GCACTGTTTGCAACAGCAAC	91	1477
803315	8261	8280	146430	146449	GTGTAAGATGCACTGTTTGC	74	1478
803316	8284	8303	146453	146472	TTTCTTTTGAATTGAGTGAA	92	1479
803317	8293	8312	146462	146481	TAATGGAGTTTTCTTTTGAA	87	1480
803318	8302	8321	146471	146490	TAGTACTTTTAATGGAGTTT	115	1481
803319	8328	8347	146497	146516	TTTGACAGTATGTCATGTTT	118	1482
803320	8337	8356	146506	146525	TATGAGGACTTTGACAGTAT	101	1483
803321	8346	8365	146515	146534	TTTCCTAGATATGAGGACTT	121	1484
803322	8355	8374	146524	146543	TTCTGTGTCTTTCCTAGATA	125	1485
803323	8373	8392	146542	146561	TTCTGTGACAAAGAGAGTTT	73	1486
803324	8382	8401	146551	146570	ACAGAGAGTTTCTGTGACAA	85	1487
803325	8391	8410	146560	146579	AGGAAAGACACAGAGAGTTT	100	1488
803326	8418	8437	146587	146606	GAGTTGAAAAACAACTCTAT	129	1489
803327	8427	8446	146596	146615	TCAAACATAGAGTTGAAAAA	116	1490
803328	8436	8455	146605	146624	TATCCACATTCAAACATAGA	116	1491
803329	8461	8480	146630	146649	TACACTAATTATACAAAATT	114	1492
803330	8470	8489	146639	146658	CACTGTATTTACACTAATTA	73	1493
803331	8479	8498	146648	146667	AGGACTGAACACTGTATTTA	56	1494
803332	8488	8507	146657	146676	ATCACTTGAAGGACTGAACA	73	1495

[0612]

[0613]

803333	8524	8543	146693	146712	ACAAGTAGCTAGTGGTATGA	85	1496
803334	8533	8552	146702	146721	GATTAGAAAACAAGTAGCTA	69	1497
803335	8545	8564	146714	146733	TAGAATGAAGCAGATTAGAA	116	1498
803336	8570	8589	146739	146758	TTAGGGAAAAGATGAATATA	93	1499
803337	8579	8598	146748	146767	ATCACAAATTTAGGGAAAAG	72	1500
803338	8588	8607	146757	146776	ATCTGCAGCATCACAAATTT	77	1501
803339	8614	8633	146783	146802	AAAGGTTTCTATCTGAATGA	107	1502
803340	8639	8658	146808	146827	GGAATTCTATAATTCTGAAA	80	1503
803341	8659	8678	146828	146847	ATGGTCTTGGTAGGAGCTGT	77	1504
803342	8668	8687	146837	146856	TTTATCCTCATGGTCTTGGT	56	1505
803343	8677	8696	146846	146865	TGTTAGATATTTATCCTCAT	66	1506
803344	8705	8724	146874	146893	GCTCCTTTCTCCTTCAGCAA	58	1507
803345	8714	8733	146883	146902	ATAACTAAAGCTCCTTTCTC	111	1508
803346	8723	8742	146892	146911	TTATCCATCATAACTAAAGC	112	1509
803347	8732	8751	146901	146920	CAGATATTTTTATCCATCAT	57	1510
803348	8750	8769	146919	146938	TTTGGAAGCCTAGGGTGGCA	80	1511
803349	8759	8778	146928	146947	TAAGTATAATTTGGAAGCCT	69	1512
803350	8768	8787	146937	146956	TAAACAATTTAAGTATAATT	121	1513
803351	8794	8813	146963	146982	TGATACTCCTATTGTGGTAA	89	1514
803352	8803	8822	146972	146991	ATTTGGCCCTGATACTCCTA	71	1515
803353	8812	8831	146981	147000	TACATAGGTATTTGGCCCTG	111	1516
803354	8838	8857	147007	147026	CTAAAGCAGAAATGACCTCA	61	1517
803355	8847	8866	147016	147035	GTACTTTTCCTAAAGCAGAA	74	1518
803356	8856	8875	147025	147044	TTACCGAAAGTACTTTTCCT	89	1519
803357	8882	8901	147051	147070	ATGAATACTGGTCAGGGCCA	102	61
803358	8891	8910	147060	147079	TCTGAAATAATGAATACTGG	85	1520
803359	8900	8919	147069	147088	AGGGAATTATCTGAAATAAT	46	1521
803360	8926	8945	147095	147114	ATTAAATGTACTAGTTGTCC	90	1522
803361	8935	8954	147104	147123	TCTGAGAATATTAAATGTAC	66	1523
803362	8944	8963	147113	147132	GCCATAAGTTCTGAGAATAT	53	1524
803363	8953	8972	147122	147141	TAGTAAAATGCCATAAGTTC	79	1525
803364	8957	8976	147126	147145	CACATAGTAAAATGCCATAA	51	1526
803365	8958	8977	147127	147146	TCACATAGTAAAATGCCATA	63	1527
803366	8959	8978	147128	147147	TTCACATAGTAAAATGCCAT	43	1528
803367	8960	8979	147129	147148	TTTCACATAGTAAAATGCCA	55	1529
803368	8961	8980	147130	147149	TTTTCACATAGTAAAATGCC	80	1530
803369	8963	8982	147132	147151	AGTTTTCACATAGTAAAATG	101	1531
803370	8964	8983	147133	147152	AAGTTTTCACATAGTAAAAT	133	1532
803371	8965	8984	147134	147153	AAAGTTTTCACATAGTAAAA	77	1533
803372	8966	8985	147135	147154	TAAAGTTTTCACATAGTAAA	88	1534
803373	8967	8986	147136	147155	TTAAAGTTTTCACATAGTAA	97	1535
803374	8972	8991	147141	147160	TAAATTTAAAGTTTTCACAT	104	1536
803375	8988	9007	147157	147176	TTACCCTTAATATAAATAAA	113	1537
803376	8997	9016	147166	147185	AGAATTTGATTACCCTTAAT	82	1538
803377	9015	9034	147184	147203	GAAAATCTTTCATCTTTAAG	116	1539
803378	9028	9047	147197	147216	CCTTTAAAATACAGAAAATC	110	1540
803379	9037	9056	147206	147225	GCATAGCTTCCTTTAAAATA	70	1541
803380	9059	9078	147228	147247	GTTAATTACATAACAAGTTA	76	1542

표 20

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	25	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	20	235
803381	9078	9097	147247	147266	TATTATATATGATTTTTTTG	96	1543
803382	9103	9122	147272	147291	GAGATAACACTGGAACAAAG	79	1544
803383	9112	9131	147281	147300	ACAATGAAAGAGATAACACT	96	1545
803384	9125	9144	147294	147313	CAAATACAAAGTAACAATGA	119	1546
803385	9164	9183	147333	147352	GTATTCATTTTTTTAATTTG	95	1547
803386	N/A	N/A	3733	3752	TACCTGCTGCACACTCGCGA	32	1548
803387	N/A	N/A	4361	4380	ATCCAAGATACATAGCAAAT	61	1549
803388	N/A	N/A	4768	4787	TAATAGTCAGATGGAAAATA	92	1550
803389	N/A	N/A	5023	5042	TATCAAGCAGGAGTGACTCT	81	1551
803390	N/A	N/A	5210	5229	CTCTCTAGGCAGAAATACTA	87	1552
803391	N/A	N/A	5227	5246	ATACTTTGCCTCTGGTACTC	80	1553
803392	N/A	N/A	5291	5310	CAACTATGATATATCCAAAA	139	1554
803393	N/A	N/A	7598	7617	AAAAGATAGGCAGGAAAAGA	185	1555
803394	N/A	N/A	8034	8053	TGCCAAACTCATCTCTGTAC	76	1556
803395	N/A	N/A	8402	8421	GTAAACAACGGCTATTTTAG	65	1557
803396	N/A	N/A	10211	10230	CCCAGAAACAAAAGCAAGCC	70	1558
803397	N/A	N/A	11602	11621	GTACTGAAAACAAGAAGAGC	96	1559
803398	N/A	N/A	11762	11781	GGACATTTAAAGTTACAATT	66	1560
803399	N/A	N/A	12023	12042	TCTTCTTCACAACTGCATGG	71	1561
803400	N/A	N/A	12348	12367	TTTACATTATTGGAAGAAGA	84	1562
803401	N/A	N/A	12349	12368	CTTTACATTATTGGAAGAAG	96	1563
803402	N/A	N/A	12350	12369	GCTTTACATTATTGGAAGAA	64	1564
803403	N/A	N/A	12351	12370	GGCTTTACATTATTGGAAGA	46	1565
803404	N/A	N/A	12352	12371	TGGCTTTACATTATTGGAAG	52	1566
803405	N/A	N/A	12354	12373	TTTGGCTTTACATTATTGGA	69	1567
803406	N/A	N/A	12355	12374	GTTTGGCTTTACATTATTGG	40	1568
803407	N/A	N/A	12356	12375	TGTTTGGCTTTACATTATTG	68	1569
803408	N/A	N/A	12357	12376	TTGTTTGGCTTTACATTATT	85	1570
803409	N/A	N/A	12358	12377	ATTGTTTGGCTTTACATTAT	57	1571
803410	N/A	N/A	13200	13219	GAATAATTCACAATGTACAC	64	1572
803411	N/A	N/A	13280	13299	CATGTGTGTTTGTTTCTTTC	70	1573
803412	N/A	N/A	14768	14787	ATTCAAACCTTCCCAATCAC	131	1574
803413	N/A	N/A	14988	15007	TCCATCGCCAAATGGAGAAT	102	1575
803414	N/A	N/A	15083	15102	AATACTGGAATAGGAGTAGT	98	1576
803415	N/A	N/A	15343	15362	TCTCATGATCCTTAGTATGA	72	1577
803416	N/A	N/A	15717	15736	ACCTGGCCTACTCCTGTTCC	95	1578

[0614]

803417	N/A	N/A	16619	16638	ATGCATATTAGTCTTTTTCC	61	1579
803418	N/A	N/A	18995	19014	CTGCCACTGTAATCACCTCT	54	1580
803419	N/A	N/A	19777	19796	TACATATTGTCTAATAATCC	114	1581
803420	N/A	N/A	20043	20062	TTTGTTGGCAGTGATGTCTC	49	1582
803421	N/A	N/A	20233	20252	TTAAAAACTTTTGATTTCTT	131	1583
803422	N/A	N/A	20684	20703	AAGGGCAACCAATGTACAAG	43	1584
803423	N/A	N/A	20708	20727	TATGACCTGTTTCCTCCATT	60	1585
803424	N/A	N/A	20709	20728	CTATGACCTGTTTCCTCCAT	82	1586
803425	N/A	N/A	20710	20729	GCTATGACCTGTTTCCTCCA	37	1587
803426	N/A	N/A	20711	20730	AGCTATGACCTGTTTCCTCC	43	1588
803427	N/A	N/A	20712	20731	CAGCTATGACCTGTTTCCTC	35	1589
803428	N/A	N/A	20714	20733	ATCAGCTATGACCTGTTTCC	69	1590
803429	N/A	N/A	20715	20734	AATCAGCTATGACCTGTTTC	70	1591
803430	N/A	N/A	20717	20736	AAAATCAGCTATGACCTGTT	72	1592
803431	N/A	N/A	20718	20737	TAAAATCAGCTATGACCTGT	88	1593
803432	N/A	N/A	21079	21098	ATGTGGTGAATATTATAGAA	38	1594
803433	N/A	N/A	21236	21255	CTTTATTGAAAATTGCCACA	43	1595
803434	N/A	N/A	22179	22198	CATTTAAGTTGGATAGTGAG	80	1596
803435	N/A	N/A	23283	23302	GGAATAAAATATACAATATA	86	1597
803436	N/A	N/A	23734	23753	AGTTCTTCTTAAAATGATCC	34	1598
803437	N/A	N/A	24259	24278	AAGCCCACATTGAAAAAACA	80	1599
803438	N/A	N/A	24494	24513	TGAAAATAAACAGAGAAGAT	93	1600
803439	N/A	N/A	24497	24516	ATGTGAAAATAAACAGAGAA	97	1601
803440	N/A	N/A	24663	24682	AGCCTAGAAGCAGTTGGTTT	88	1602
803441	N/A	N/A	25966	25985	AATAATAACAATATCCCATC	83	1603
803442	N/A	N/A	26005	26024	AAGATTGATGAACCACAGGA	51	1604
803443	N/A	N/A	26046	26065	ATTTCATCCCTTACTGCTTA	123	1605
803444	N/A	N/A	26583	26602	AGAGATAATCAAGAGAAAAA	104	1606
803445	N/A	N/A	27062	27081	AGTATGGAGCTCCTTTACCA	66	1607
803446	N/A	N/A	28223	28242	TACATTGAGATGTGTATATT	111	1608
803447	N/A	N/A	29215	29234	TGCTTTAGGAGAAGCCTTGG	62	1609
803448	N/A	N/A	29216	29235	GTGCTTTAGGAGAAGCCTTG	41	1610
803449	N/A	N/A	29217	29236	TGTGCTTTAGGAGAAGCCTT	36	1611
803450	N/A	N/A	29218	29237	GTGTGCTTTAGGAGAAGCCT	34	1612
803451	N/A	N/A	29219	29238	GGTGTGCTTTAGGAGAAGCC	40	1613
803452	N/A	N/A	29221	29240	GAGGTGTGCTTTAGGAGAAG	58	1614
803453	N/A	N/A	29222	29241	TGAGGTGTGCTTTAGGAGAA	56	1615
803454	N/A	N/A	29223	29242	ATGAGGTGTGCTTTAGGAGA	80	1616
803455	N/A	N/A	29224	29243	AATGAGGTGTGCTTTAGGAG	68	1617
803456	N/A	N/A	29225	29244	GAATGAGGTGTGCTTTAGGA	63	1618
803457	N/A	N/A	29927	29946	ATTTTAAAACGATCAGCCAG	87	1619

표 21

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

[0615]

[0616]

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	16	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	28	235
803458	N/A	N/A	30062	30081	AGTTGGGAACTCATCATAGG	79	1620
803459	N/A	N/A	30238	30257	AGGCTCACGGATATGAAACA	59	1621
803460	N/A	N/A	30698	30717	AAGAGAGGAAAAACTGAAAA	83	1622
803461	N/A	N/A	31335	31354	GTTTACACATAGAAGTCCGG	46	1623
803462	N/A	N/A	32129	32148	TAAAGGGATACAAGCCATTT	74	1624
803463	N/A	N/A	32534	32553	TCCTTGAGAGCAGCCCCTGT	76	1625
803464	N/A	N/A	32577	32596	ATTCGAGAACAGCGATTCCC	100	1626
803465	N/A	N/A	32857	32876	ACTGAACAAAGACATCAGGG	36	1627
803466	N/A	N/A	32987	33006	ATGAACGAGCTACTCAAGTT	79	1628
803467	N/A	N/A	32997	33016	AAGAAAGTTGATGAACGAGC	48	1629
803468	N/A	N/A	33091	33110	CCTGCCAATGTAGCCATTTT	40	1630
803469	N/A	N/A	33163	33182	GAATAGGAAAAATGTCACAC	39	1631
803470	N/A	N/A	33422	33441	GTCTTACTCAATAGTCACCT	25	1632
803471	N/A	N/A	33499	33518	TCTTGATCTCATCCACTCCA	44	1633
803472	N/A	N/A	35580	35599	CAAGTGTCTTATGTTTTTCT	42	1634
803473	N/A	N/A	35803	35822	GATTTTATCTTTTATAACTT	75	1635
803474	N/A	N/A	36736	36755	TCTGTTTACTTATCAGTCTC	77	1636
803475	N/A	N/A	37002	37021	GCAGTAGGTACTATGAACTT	36	1637
803476	N/A	N/A	38011	38030	CTTGAACTCAGGTCATGGCA	69	1638
803477	N/A	N/A	38572	38591	CTCACCCCCGACCATGTGCA	71	1639
803478	N/A	N/A	38768	38787	CACAATGCTATTGTCTTTAG	72	1640
803479	N/A	N/A	39901	39920	CATAATGTACATCTTTGCCA	59	1641
803480	N/A	N/A	40030	40049	AATGTCTATATAACAAGTTA	80	1642
803481	N/A	N/A	40156	40175	TATATCCCTTCTTAAAGAAT	94	1643
803482	N/A	N/A	40684	40703	CGTGTGGACTGTAAATTTTT	91	1644
803483	N/A	N/A	40840	40859	CATCATGCTACATGTAATGG	59	1645
803484	N/A	N/A	41078	41097	TGCTGGGAATACTATGGTAA	64	1646
803485	N/A	N/A	41108	41127	ATTCCAATTACATGCCAAGG	49	1647
803486	N/A	N/A	41173	41192	ATCTGCATTAATGCAAACTG	71	1648
803487	N/A	N/A	41893	41912	ATTCTTCTGGCATGCCTAAA	75	1649
803488	N/A	N/A	42134	42153	TCATCTTATGTCTCTAACCA	68	1650
803489	N/A	N/A	44968	44987	TACTTTGCTGAGTACCATCC	54	1651
803490	N/A	N/A	45375	45394	AGGAAGTAACCATGTCCTCA	38	1652
803491	N/A	N/A	45376	45395	AAGGAAGTAACCATGTCCTC	58	1653
803492	N/A	N/A	45377	45396	AAAGGAAGTAACCATGTCCT	57	1654
803493	N/A	N/A	45378	45397	AAAAGGAAGTAACCATGTCC	93	1655
803494	N/A	N/A	45379	45398	TAAAAGGAAGTAACCATGTC	92	1656
803495	N/A	N/A	45381	45400	ATTAAAAGGAAGTAACCATG	78	1657
803496	N/A	N/A	45382	45401	TATTAAAAGGAAGTAACCAT	90	1658
803497	N/A	N/A	45383	45402	GTATTAAAAGGAAGTAACCA	86	1659

803498	N/A	N/A	45384	45403	GGTATTAAAAGGAAGTAACC	34	1660
803499	N/A	N/A	45385	45404	AGGTATTAAAAGGAAGTAAC	50	1661
803500	N/A	N/A	46126	46145	TATGTATCCAAACATGGATT	71	1662
803501	N/A	N/A	46232	46251	GGTGACAAAGTCTTCATCTG	58	1663
803502	N/A	N/A	46931	46950	TTTATTTGAGTCTATTTCCT	79	1664
803503	N/A	N/A	48097	48116	GGGTGCATAGTCTGTAGGTA	32	1665
803504	N/A	N/A	48768	48787	GGATTTCAAGAGAAAAAATC	93	1666
803505	N/A	N/A	48918	48937	ATATCTTTACCATGTATATG	88	1667
803506	N/A	N/A	49003	49022	TCCAAACTCAGAATGCACCA	42	1668
803507	N/A	N/A	49316	49335	GTCTATGAGTAATGGCATGG	47	1669
803508	N/A	N/A	49674	49693	GGATTAAAATCAATTTATCA	80	1670
803509	N/A	N/A	50436	50455	AATTTCTTTTGGCTTGATAC	89	1671
803510	N/A	N/A	51368	51387	TTCAAATTATGCGAATCTGA	66	1672
803511	N/A	N/A	51478	51497	TTGGACATCATTTCATTTAT	48	1673
803512	N/A	N/A	52070	52089	ACCTTAAAAGCCCAGGATCT	85	1674
803513	N/A	N/A	52149	52168	ACTTTAAAGATGCAGAAATA	80	1675
803514	N/A	N/A	52150	52169	AACTTTAAAGATGCAGAAAT	92	1676
803515	N/A	N/A	52151	52170	AAACTTTAAAGATGCAGAAA	111	1677
803516	N/A	N/A	52152	52171	CAAACTTTAAAGATGCAGAA	63	1678
803517	N/A	N/A	52153	52172	CCAAACTTTAAAGATGCAGA	28	1679
803518	N/A	N/A	52155	52174	TGCCAAACTTTAAAGATGCA	40	1680
803519	N/A	N/A	52156	52175	TTGCCAAACTTTAAAGATGC	30	1681
803520	N/A	N/A	52157	52176	TTTGCCAAACTTTAAAGATG	63	1682
803521	N/A	N/A	52158	52177	GTTTGCCAAACTTTAAAGAT	50	1683
803522	N/A	N/A	52159	52178	GGTTTGCCAAACTTTAAAGA	39	1684
803523	N/A	N/A	52305	52324	CCAAATATGTTTCACCCCAG	78	1685
803524	N/A	N/A	52501	52520	AGCATTTTTACAATTAAGGA	59	1686
803525	N/A	N/A	53088	53107	CATACTTTAGTCTGTATTTC	69	1687
803526	N/A	N/A	53538	53557	TTATTATATATCATGTTTTA	83	1688
803527	N/A	N/A	53539	53558	GTTATTATATATCATGTTTT	62	1689
803528	N/A	N/A	53540	53559	AGTTATTATATATCATGTTT	55	1690
803529	N/A	N/A	53541	53560	CAGTTATTATATATCATGTT	55	1691
803530	N/A	N/A	53542	53561	ACAGTTATTATATATCATGT	33	1692
803531	N/A	N/A	53544	53563	AGACAGTTATTATATATCAT	49	1693
803532	N/A	N/A	53545	53564	AAGACAGTTATTATATATCA	64	1694
803533	N/A	N/A	53546	53565	AAAGACAGTTATTATATATC	80	1695
803534	N/A	N/A	53547	53566	CAAAGACAGTTATTATATAT	100	1696

표 22

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시	서열 번호: 1 중단	서열 번호: 2 개시	서열 번호: 2 중단	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호

[0617]

	부위	부위	부위	부위			
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	20	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	19	235
803535	N/A	N/A	53548	53567	ACAAAGACAGTTATTATATA	107	1697
803536	N/A	N/A	54011	54030	TTCCTGAGTCAGCTGGGCAC	74	1698
803537	N/A	N/A	55467	55486	GTTGAGTGTAGTTGAGAAGC	49	1699
803538	N/A	N/A	55699	55718	AAAGATGCTTGTCTAAAGCC	51	1700
803539	N/A	N/A	55823	55842	AATAAATACTCCCTCTCTCT	89	1701
803540	N/A	N/A	56181	56200	ACTAAAAAGAGTGGAAATGA	98	1702
803541	N/A	N/A	57300	57319	GGCAAACATAGTACTTTATT	27	1703
803542	N/A	N/A	57536	57555	TGTTGCTTGCTTAAAAGAAA	87	1704
803543	N/A	N/A	59667	59686	TACTGCTCACAGATATTTAT	82	1705
803544	N/A	N/A	59986	60005	CTCTTGTCAATGCCCTACAC	64	1706
803545	N/A	N/A	60613	60632	GCAAAAAGGTGTTCATTCTT	71	1707
803546	N/A	N/A	60625	60644	ACTTTTCACCCAGCAAAAAG	106	1708
803547	N/A	N/A	60658	60677	ATGCTATTTCTATTACCCCA	58	1709
803548	N/A	N/A	61404	61423	ACCTTCCTCTAAATGTTATG	87	1710
803549	N/A	N/A	61573	61592	CTGTCCTGCCTTTATTTGTG	86	1711
803550	N/A	N/A	62233	62252	TGTTACTTACTTGTTTGTTT	108	1712
803551	N/A	N/A	63413	63432	TTGACTTCATGGTACTAACA	76	1713
803552	N/A	N/A	63832	63851	CAAAGCATTCCACAACATGT	65	1714
803553	N/A	N/A	63953	63972	TGCATTTTCATCAACATTAG	59	1715
803554	N/A	N/A	64097	64116	TTTTTGGCATAAGACTAGTT	79	1716
803555	N/A	N/A	64246	64265	TCTATGTTTTTTTAACTGGG	40	1717
803556	N/A	N/A	64593	64612	CAACAGTAGGAATAGCAATA	98	1718
803557	N/A	N/A	64954	64973	GTTTGCTGAGTGATTCATTA	59	1719
803558	N/A	N/A	66316	66335	AATGGTTTGACTTGAGACAC	52	1720
803559	N/A	N/A	66412	66431	AATTTTCAAAGCGCATGAAA	92	1721
803560	N/A	N/A	66414	66433	TTAATTTTCAAAGCGCATGA	45	1722
803561	N/A	N/A	66415	66434	GTTAATTTTCAAAGCGCATG	29	1723
803562	N/A	N/A	66416	66435	TGTTAATTTTCAAAGCGCAT	29	1724
803563	N/A	N/A	66418	66437	TATGTTAATTTTCAAAGCGC	32	1725
803564	N/A	N/A	66419	66438	ATATGTTAATTTTCAAAGCG	96	1726
803565	N/A	N/A	66420	66439	AATATGTTAATTTTCAAAGC	90	1727
803566	N/A	N/A	66421	66440	GAATATGTTAATTTTCAAAG	100	1728
803567	N/A	N/A	66422	66441	TGAATATGTTAATTTTCAAA	112	1729
803568	N/A	N/A	66672	66691	AGAATGCTCATGTACTGCTG	43	1730
803569	N/A	N/A	66673	66692	CAGAATGCTCATGTACTGCT	55	1731
803570	N/A	N/A	66911	66930	CTGTCACAACTTCTATCTAG	69	1732
803571	N/A	N/A	67066	67085	GTTTCTTAAGTGGGATACAA	25	1733
803572	N/A	N/A	67163	67182	ACTTAAAATGTTTTAGACCT	88	1734
803573	N/A	N/A	68270	68289	AATACCTCAGCAGATGCTGA	81	1735
803574	N/A	N/A	68715	68734	CACATTACTAAAACTGACTT	78	1736
803575	N/A	N/A	68989	69008	AAACCAGTGTTCTAAGCTTC	64	1737
803576	N/A	N/A	70079	70098	AAATGATACTAACTGCAAAC	85	1738

[0618]

803577	N/A	N/A	70083	70102	AAGAAAATGATACTAACTGC	78	1739
803578	N/A	N/A	70146	70165	TAATCTGCATATGGGTTTCT	36	1740
803579	N/A	N/A	70615	70634	AGATTATTAAATTATCATAA	112	1741
803580	N/A	N/A	71056	71075	TATTTGAATTTCATGTTTCA	54	1742
803581	N/A	N/A	71205	71224	TTTTTATGGAGACCGCTGGA	77	1743
803582	N/A	N/A	71512	71531	GTCCATTCCCTTTGTAAAAT	53	1744
803583	N/A	N/A	71525	71544	TGGAAATTTCACAGTCCATT	30	1745
803584	N/A	N/A	72654	72673	TCATTAACCAAACTACTTTT	106	1746
803585	N/A	N/A	72790	72809	ATTATGAGGATAAAAGAAAA	125	1747
803586	N/A	N/A	72791	72810	AATTATGAGGATAAAAGAAA	121	1748
803587	N/A	N/A	72792	72811	CAATTATGAGGATAAAAGAA	117	1749
803588	N/A	N/A	72793	72812	CCAATTATGAGGATAAAAGA	92	1750
803589	N/A	N/A	72794	72813	CCCAATTATGAGGATAAAAG	49	1751
803590	N/A	N/A	72796	72815	AACCCAATTATGAGGATAAA	81	1752
803591	N/A	N/A	72797	72816	GAACCCAATTATGAGGATAA	60	1753
803592	N/A	N/A	72798	72817	AGAACCCAATTATGAGGATA	85	1754
803593	N/A	N/A	72799	72818	AAGAACCCAATTATGAGGAT	99	1755
803594	N/A	N/A	72800	72819	TAAGAACCCAATTATGAGGA	89	1756
803595	N/A	N/A	73940	73959	AGATCTGTTTCCATTGCCTG	24	1757
803596	N/A	N/A	74241	74260	CTTTAAGTTACACATTATTT	44	1758
803597	N/A	N/A	74300	74319	CAAACTATGTTATACTTTAA	92	1759
803598	N/A	N/A	76344	76363	ACTCTTCAGAGTCTGAAAAG	79	1760
803599	N/A	N/A	76345	76364	AACTCTTCAGAGTCTGAAAA	71	1761
803600	N/A	N/A	76346	76365	AAACTCTTCAGAGTCTGAAA	71	1762
803601	N/A	N/A	76347	76366	CAAACTCTTCAGAGTCTGAA	67	1763
803602	N/A	N/A	76348	76367	TCAAACTCTTCAGAGTCTGA	62	1764
803603	N/A	N/A	76350	76369	TGTCAAACTCTTCAGAGTCT	20	1765
803604	N/A	N/A	76351	76370	GTGTCAAACTCTTCAGAGTC	16	1766
803605	N/A	N/A	77606	77625	ATAGTTGGGAACGAATAGTA	61	1767
803606	N/A	N/A	77607	77626	TATAGTTGGGAACGAATAGT	89	1768
803607	N/A	N/A	77608	77627	TTATAGTTGGGAACGAATAG	94	1769
803608	N/A	N/A	77609	77628	CTTATAGTTGGGAACGAATA	72	1770
803609	N/A	N/A	77610	77629	TCTTATAGTTGGGAACGAAT	65	1771
803610	N/A	N/A	77612	77631	TGTCTTATAGTTGGGAACGA	36	1772
803611	N/A	N/A	77613	77632	ATGTCTTATAGTTGGGAACG	32	1773

표 23

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	12	235

[0619]

780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	11	235
780617	N/A	N/A	81581	81600	GTTTGAAGGAATAGCTGACA	35	667
			87838	87857			
780618	N/A	N/A	81584	81603	AGTGTTTGAAGGAATAGCTG	25	668
			87841	87860			
780619	N/A	N/A	81587	81606	CATAGTGTTTGAAGGAATAG	62	669
			87844	87863			
780620	N/A	N/A	81590	81609	AGCCATAGTGTTTGAAGGAA	11	670
			87847	87866			
780621	N/A	N/A	81593	81612	AAAAGCCATAGTGTTTGAAG	55	671
			87850	87869			
780622	N/A	N/A	81596	81615	CTAAAAAGCCATAGTGTTTG	69	672
			87853	87872			
780623	N/A	N/A	81599	81618	ATTCTAAAAAGCCATAGTGT	45	673
			87856	87875			
780624	N/A	N/A	81630	81649	GCAGCATCATGCAAGCAGCA	12	674
			87887	87906			
780625	N/A	N/A	81633	81652	ATTGCAGCATCATGCAAGCA	40	675
			87890	87909			
803612	N/A	N/A	77614	77633	AATGTCTTATAGTTGGGAAC	36	1774
803613	N/A	N/A	77615	77634	GAATGTCTTATAGTTGGGAA	45	1775
803614	N/A	N/A	77616	77635	AGAATGTCTTATAGTTGGGA	30	1776
803615	N/A	N/A	78807	78826	TAAGGACAGAGACCGAGTTT	58	1777
803616	N/A	N/A	79332	79351	CATTTACATGGGATTATTTT	56	1778
803617	N/A	N/A	79675	79694	ATAGCTATTATACCTCACCT	52	1779
803618	N/A	N/A	79976	79995	ATTGTTAAGAAGGAAATGCA	70	1780
803619	N/A	N/A	80327	80346	ACTCTGGTATATTTTATGAT	N/A	1781
803620	N/A	N/A	80378	80397	AGAGATTGGGAAACATTCAG	38	1782
803621	N/A	N/A	80523	80542	TATAGCAAAACAACTATGAA	84	1783
803622	N/A	N/A	81353	81372	CCCCAAAATTTCACTCAAAC	55	1784
803623	N/A	N/A	81582	81601	TGTTTGAAGGAATAGCTGAC	50	1785
			87839	87858			
803624	N/A	N/A	81583	81602	GTGTTTGAAGGAATAGCTGA	39	1786
			87840	87859			
803625	N/A	N/A	81585	81604	TAGTGTTTGAAGGAATAGCT	48	1787
			87842	87861			
803626	N/A	N/A	81586	81605	ATAGTGTTTGAAGGAATAGC	48	1788
			87843	87862			
803627	N/A	N/A	81588	81607	CCATAGTGTTTGAAGGAATA	26	1789
			87845	87864			
803628	N/A	N/A	81589	81608	GCCATAGTGTTTGAAGGAAT	12	1790
			87846	87865			
803629	N/A	N/A	81591	81610	AAGCCATAGTGTTTGAAGGA	19	1791
			87848	87867			
803630	N/A	N/A	81592	81611	AAAGCCATAGTGTTTGAAGG	34	1792
			87849	87868			
803631	N/A	N/A	81594	81613	AAAAAGCCATAGTGTTTGAA	56	1793
			87851	87870			

[0620]

803632	N/A	N/A	81595 87852	81614 87871	TAAAAAGCCATAGTGTTTGA	76	1794
803633	N/A	N/A	81597 87854	81616 87873	TCTAAAAAGCCATAGTGTTT	58	1795
803634	N/A	N/A	81598 87855	81617 87874	TTCTAAAAAGCCATAGTGTT	71	1796
803635	N/A	N/A	81625	81644	ATCATGCAAGCAGCATTTTA	63	1797
803636	N/A	N/A	81626	81645	CATCATGCAAGCAGCATTTT	82	1798
803637	N/A	N/A	81627	81646	GCATCATGCAAGCAGCATTT	23	1799
803638	N/A	N/A	81628	81647	AGCATCATGCAAGCAGCATT	25	1800
803639	N/A	N/A	81629	81648	CAGCATCATGCAAGCAGCAT	34	1801
803640	N/A	N/A	81631 87888	81650 87907	TGCAGCATCATGCAAGCAGC	16	1802
803641	N/A	N/A	81632 87889	81651 87908	TTGCAGCATCATGCAAGCAG	31	1803
803642	N/A	N/A	81634 87891	81653 87910	CATTGCAGCATCATGCAAGC	44	1804
803643	N/A	N/A	81635 87892	81654 87911	TCATTGCAGCATCATGCAAG	43	1805
803644	N/A	N/A	81822	81841	GGAGATAATAACAGTGGCTA	48	1806
803645	N/A	N/A	82500	82519	GTGGAAGTATTAAGGCTACT	14	1807
803646	N/A	N/A	82501	82520	AGTGGAAGTATTAAGGCTAC	23	1808
803647	N/A	N/A	82502	82521	TAGTGGAAGTATTAAGGCTA	20	1809
803648	N/A	N/A	82503	82522	TTAGTGGAAGTATTAAGGCT	36	1810
803649	N/A	N/A	82504	82523	TTTAGTGGAAGTATTAAGGC	43	1811
803650	N/A	N/A	82506	82525	TGTTTAGTGGAAGTATTAAG	32	1812
803651	N/A	N/A	82507	82526	TTGTTTAGTGGAAGTATTAA	81	1813
803652	N/A	N/A	82508	82527	ATTGTTTAGTGGAAGTATTA	60	1814
803653	N/A	N/A	82509	82528	TATTGTTTAGTGGAAGTATT	62	1815
803654	N/A	N/A	82510	82529	TTATTGTTTAGTGGAAGTAT	36	1816
803655	N/A	N/A	82697	82716	TTGTCATAGTTAAGTAACAG	20	1817
803656	N/A	N/A	83102	83121	AAACAAGTAATACAGTATAC	83	1818
803657	N/A	N/A	83213	83232	ATTTCAGATTTACAACAGAG	70	1819
803658	N/A	N/A	85777	85796	TGTTAAAGCTTGATAATAGG	49	1820
803659	N/A	N/A	86988	87007	AGCACCAAATTGTTCCTAAC	62	1821
803660	N/A	N/A	89783	89802	AGCACACATAATCTATATAA	34	1822
803661	N/A	N/A	89916	89935	TACCATCTATCATCAATAAA	26	1823
803662	N/A	N/A	90146	90165	TTCTCTGACAACAATGACAA	62	1824
803663	N/A	N/A	90678	90697	TGTCTGCACAGACACCTGTT	87	1825
803664	N/A	N/A	91038	91057	GTATCTCTTAACCCAGAGAA	37	1826
803665	N/A	N/A	91039	91058	TGTATCTCTTAACCCAGAGA	17	1827
803666	N/A	N/A	91040	91059	ATGTATCTCTTAACCCAGAG	24	1828
803667	N/A	N/A	91041	91060	CATGTATCTCTTAACCCAGA	36	1829
803668	N/A	N/A	91042	91061	TCATGTATCTCTTAACCCAG	37	1830
803669	N/A	N/A	91044	91063	TTTCATGTATCTCTTAACCC	26	1831
803670	N/A	N/A	91045	91064	TTTTCATGTATCTCTTAACC	58	1832
803671	N/A	N/A	91046	91065	GTTTTCATGTATCTCTTAAC	20	1833
803672	N/A	N/A	91047	91066	TGTTTTCATGTATCTCTTAA	36	1834

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803673	N/A	N/A	91048	91067	CTGTTTTCATGTATCTCTTA	21	1835
803674	N/A	N/A	91144	91163	AAATTAACTTGGTCTTTTTC	68	1836
803675	N/A	N/A	91456	91475	TCTGTTGCTCTTAGAATCTA	23	1837
803676	N/A	N/A	91530	91549	ATGGAACCTTGAACTTGGGA	25	1838
803677	N/A	N/A	92329	92348	GATTCAGAAACACTTTTATA	59	1839
803678	N/A	N/A	92773	92792	AAGTTGCTTTGAGAATTTTC	48	1840
803679	N/A	N/A	93235	93254	AAATCTAGTCCAACTTCCTC	78	1841

표 24

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	18	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	20	235
803680	N/A	N/A	93932	93951	ACTCATTGGTAATGGATTAT	24	1842
803681	N/A	N/A	94454	94473	TTGCAATGTTTCAATATGCT	53	1843
803682	N/A	N/A	94455	94474	ATTGCAATGTTTCAATATGC	26	1844
803683	N/A	N/A	94456	94475	GATTGCAATGTTTCAATATG	58	1845
803684	N/A	N/A	94457	94476	TGATTGCAATGTTTCAATAT	65	1846
803685	N/A	N/A	94458	94477	CTGATTGCAATGTTTCAATA	53	1847
803686	N/A	N/A	94460	94479	TGCTGATTGCAATGTTTCAA	24	1848
803687	N/A	N/A	94461	94480	TTGCTGATTGCAATGTTTCA	57	1849
803688	N/A	N/A	94462	94481	ATTGCTGATTGCAATGTTTC	59	1850
803689	N/A	N/A	94463	94482	AATTGCTGATTGCAATGTTT	54	1851
803690	N/A	N/A	94464	94483	TAATTGCTGATTGCAATGTT	75	1852
803691	N/A	N/A	95362	95381	AATCGGAAATTTAAATTATC	104	1853
803692	N/A	N/A	95619	95638	TTAGTGACCTAACAGCTCGG	64	1854
803693	N/A	N/A	97048	97067	GTACAGTATTTATTGAATCA	27	1855
803694	N/A	N/A	97142	97161	ATTTATGCTATCATGTAGTT	71	1856
803695	N/A	N/A	97748	97767	AATAATATATTCCCAGGAAA	90	1857
803696	N/A	N/A	97935	97954	TAGCAACCATGTGGCCTAGA	59	1858
803697	N/A	N/A	98088	98107	ACTGTCAAAATCTGAAAGAT	92	1859
803698	N/A	N/A	98337	98356	AGTTAGTTTGACAATTAAAA	72	1860
803699	N/A	N/A	98486	98505	AGTAACTATACACATAAAGT	99	1861
803700	N/A	N/A	99619	99638	CACCGGATTTGCTCTTTTTT	30	1862
803701	N/A	N/A	100073	100092	AATCTACTGCACACAACACA	89	1863
803702	N/A	N/A	100118	100137	AATGGAGCCATTAATTATTA	95	1864
803703	N/A	N/A	100281	100300	ATTTCCTTACCTTTTCTACA	103	1865
803704	N/A	N/A	100353	100372	GCTTTAAGGTAAAGTTTTTT	33	1866
803705	N/A	N/A	100816	100835	GCCAGCATTCAAACCCTCAA	39	1867
803706	N/A	N/A	102479	102498	ATGAGAGTAGATTTTAATAG	85	1868

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803707	N/A	N/A	102841	102860	CTGAGTTCCAAAGCATTTAA	80	1869
803708	N/A	N/A	103029	103048	CACATTTTAATGCAGGAAAA	97	1870
803709	N/A	N/A	105168	105187	TGGATATAAGTGAATACACA	71	1871
803710	N/A	N/A	105655	105674	ATAGTGGCCCCTAAATCCTT	83	1872
803711	N/A	N/A	105656	105675	TATAGTGGCCCCTAAATCCT	79	1873
803712	N/A	N/A	105657	105676	ATATAGTGGCCCCTAAATCC	73	1874
803713	N/A	N/A	105658	105677	CATATAGTGGCCCCTAAATC	88	1875
803714	N/A	N/A	105659	105678	TCATATAGTGGCCCCTAAAT	80	1876
803715	N/A	N/A	105661	105680	AGTCATATAGTGGCCCCTAA	46	1877
803716	N/A	N/A	105662	105681	TAGTCATATAGTGGCCCCTA	58	1878
803717	N/A	N/A	105663	105682	ATAGTCATATAGTGGCCCCT	57	1879
803718	N/A	N/A	105664	105683	CATAGTCATATAGTGGCCCC	49	1880
803719	N/A	N/A	105665	105684	CCATAGTCATATAGTGGCCC	35	1881
803720	N/A	N/A	105789	105808	CTTCCAACTCATTCTCTCTC	75	1882
803721	N/A	N/A	105839	105858	GTGGCCTCAGAGCTTTCTGC	62	1883
803722	N/A	N/A	105902	105921	TCCACTGTGTAGCCTCATTT	103	1884
803723	N/A	N/A	106062	106081	AAGCCACATTTATTACCTTT	49	1885
803724	N/A	N/A	106724	106743	GAGAAATAACACAAAACTTT	101	1886
803725	N/A	N/A	106922	106941	GGCACTGAAAAGTCCCAAGT	28	1887
803726	N/A	N/A	107295	107314	AGTAGGAAATAGGATAAGCA	79	1888
803727	N/A	N/A	108334	108353	TTAACATGTAAGGACTGAAA	97	1889
803728	N/A	N/A	108377	108396	TGATGACATATCCACCACAT	84	1890
803729	N/A	N/A	108774	108793	TTTAGCTTACTACTATATAT	91	1891
803730	N/A	N/A	109150	109169	TAATGCAAGTAATACAAAAA	102	1892
803731	N/A	N/A	109281	109300	TTCTTTAACAATCAATAGAG	79	1893
803732	N/A	N/A	109893	109912	TATGGATGAAAAGTGAACAT	91	1894
803733	N/A	N/A	110855	110874	GAAATTACCTACACATTAAA	103	1895
803734	N/A	N/A	110955	110974	GACATTTTTAATGTACTAAT	63	1896
803735	N/A	N/A	111205	111224	AATTTTCTATCCTGGAAAAG	95	1897
803736	N/A	N/A	111262	111281	AGAAGGAGTTAAGTTAGCTC	51	1898
803737	N/A	N/A	112344	112363	CAGTGTAGTCATACTAACAG	58	1899
803738	N/A	N/A	112345	112364	ACAGTGTAGTCATACTAACA	54	1900
803739	N/A	N/A	112346	112365	CACAGTGTAGTCATACTAAC	58	1901
803740	N/A	N/A	112347	112366	ACACAGTGTAGTCATACTAA	31	1902
803741	N/A	N/A	112348	112367	CACACAGTGTAGTCATACTA	38	1903
803742	N/A	N/A	112350	112369	TGCACACAGTGTAGTCATAC	35	1904
803743	N/A	N/A	112351	112370	GTGCACACAGTGTAGTCATA	30	1905
803744	N/A	N/A	112352	112371	AGTGCACACAGTGTAGTCAT	27	1906
803745	N/A	N/A	112353	112372	CAGTGCACACAGTGTAGTCA	19	1907
803746	N/A	N/A	112354	112373	ACAGTGCACACAGTGTAGTC	45	1908
803747	N/A	N/A	112629	112648	CTTGCTTTATGGTAAGAATG	46	1909
803748	N/A	N/A	113302	113321	CAAGTCTGGATCACACTTGT	71	1910
803749	N/A	N/A	113398	113417	AAAATTTGATCAGGGAAATG	102	1911
803750	N/A	N/A	113772	113791	GTGGAATAGTGATGAATCCC	35	1912
803751	N/A	N/A	113824	113843	AGACTATTTAAAAAATGGGA	77	1913
803752	N/A	N/A	114604	114623	CACAGTAATTCTGAAGGCTT	64	1914
803753	N/A	N/A	114621	114640	CCTTCCCCTACTGTCAACAC	80	1915
803754	N/A	N/A	114658	114677	CCCCAGGCACTGTTTTCCTT	92	1916

[0623]

803755	N/A	N/A	115071	115090	GTTTCAGAGAACTAGAATAA	65	1917
803756	N/A	N/A	115110	115129	ACTTCATCAGAAACTGCTGG	48	1918

표 25

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	24	235
780254	4111	4130	86606	86625	GTTTCATTCGGTTATAAGGC	26	235
803757	N/A	N/A	117459	117478	AAAATTCTGATTTCCAACTC	94	1919
803758	N/A	N/A	118016	118035	GTATGTTAAATAAGAATTGA	99	1920
803759	N/A	N/A	118692	118711	CAATGTGATGCTTGCATTTT	87	1921
803760	N/A	N/A	118987	119006	TGACACCAAATTAGTCATTT	55	1922
803761	N/A	N/A	119091	119110	TGTACTCAAACATGTATATA	75	1923
803762	N/A	N/A	119108	119127	GGTCACGGCCAGCCCCCTGT	95	1924
803763	N/A	N/A	119608	119627	AACATACACTTTGAAGTGTT	62	1925
803764	N/A	N/A	119902	119921	GTTTAGGAGAGACTATAGAA	73	1926
803765	N/A	N/A	119903	119922	GGTTTAGGAGAGACTATAGA	42	1927
803766	N/A	N/A	119904	119923	TGGTTTAGGAGAGACTATAG	43	1928
803767	N/A	N/A	119905	119924	ATGGTTTAGGAGAGACTATA	43	1929
803768	N/A	N/A	119906	119925	TATGGTTTAGGAGAGACTAT	49	1930
803769	N/A	N/A	119908	119927	CATATGGTTTAGGAGAGACT	28	1931
803770	N/A	N/A	119909	119928	GCATATGGTTTAGGAGAGAC	8	1932
803771	N/A	N/A	119910	119929	TGCATATGGTTTAGGAGAGA	14	1933
803772	N/A	N/A	119911	119930	TTGCATATGGTTTAGGAGAG	40	1934
803773	N/A	N/A	119912	119931	GTTGCATATGGTTTAGGAGA	21	1935
803774	N/A	N/A	120040	120059	TCTATGGAATTTCATCCTTT	62	1936
803775	N/A	N/A	120380	120399	CAGCAAAACCAGGAAGTCAG	75	1937
803776	N/A	N/A	121866	121885	GTATTGTTGCCAAATGAATG	50	1938
803777	N/A	N/A	121867	121886	TGTATTGTTGCCAAATGAAT	64	1939
803778	N/A	N/A	121868	121887	ATGTATTGTTGCCAAATGAA	66	1940
803779	N/A	N/A	121869	121888	AATGTATTGTTGCCAAATGA	77	1941
803780	N/A	N/A	121870	121889	CAATGTATTGTTGCCAAATG	56	1942
803781	N/A	N/A	121872	121891	TTCAATGTATTGTTGCCAAA	49	1943
803782	N/A	N/A	121873	121892	GTTCAATGTATTGTTGCCAA	21	1944
803783	N/A	N/A	121874	121893	TGTTCAATGTATTGTTGCCA	43	1945
803784	N/A	N/A	121875	121894	ATGTTCAATGTATTGTTGCC	38	1946
803785	N/A	N/A	121876	121895	AATGTTCAATGTATTGTTGC	57	1947
803786	N/A	N/A	122268	122287	CACATCCTTTTACAATAGTT	46	1948
803787	N/A	N/A	123076	123095	AGGATGGAGACATCGAATTT	67	1949
803788	N/A	N/A	123077	123096	AAGGATGGAGACATCGAATT	78	1950

[0624]

803789	N/A	N/A	123078	123097	GAAGGATGGAGACATCGAAT	45	1951
803790	N/A	N/A	123079	123098	GGAAGGATGGAGACATCGAA	46	1952
803791	N/A	N/A	123080	123099	TGGAAGGATGGAGACATCGA	67	1953
803792	N/A	N/A	123082	123101	GTTGGAAGGATGGAGACATC	65	1954
803793	N/A	N/A	123083	123102	AGTTGGAAGGATGGAGACAT	54	1955
803794	N/A	N/A	123084	123103	GAGTTGGAAGGATGGAGACA	67	1956
803795	N/A	N/A	123085	123104	AGAGTTGGAAGGATGGAGAC	82	1957
803796	N/A	N/A	123086	123105	AAGAGTTGGAAGGATGGAGA	99	1958
803797	N/A	N/A	124014	124033	TGGATAGACAGAAAGTTATC	89	1959
803798	N/A	N/A	124460	124479	TCCAGGACAGTGTTTTAAAA	57	1960
803799	N/A	N/A	125043	125062	AATCTTCATTGTAGAGAAAA	96	1961
803800	N/A	N/A	125214	125233	GCGGATTTTTTAAAAAGCCT	44	1962
803801	N/A	N/A	126287	126306	TAAAAAGAGACCCAAATAAC	108	1963
803802	N/A	N/A	126714	126733	TTTAATTCTGTCTCTGTGTG	88	1964
803803	N/A	N/A	127951	127970	GCTTGAGAAGACCTAAGTAA	72	1965
803804	N/A	N/A	128819	128838	GATGGTAACCTAAATTAAAA	87	1966
803805	N/A	N/A	129120	129139	AGAGCTGTGACATGGCCACC	74	1967
803806	N/A	N/A	129202	129221	TCTCTAGATTCTGTTTTTGA	97	1968
803807	N/A	N/A	129512	129531	CTGGAACCCAACTAGATCAC	78	1969
803808	N/A	N/A	129985	130004	TGATTCTAAAGCAAAACACA	96	1970
803809	N/A	N/A	130212	130231	CTTGCCTGGCAGTGGGAAAA	120	1971
803810	N/A	N/A	130229	130248	AATGAAAGACTGGCTCCCTT	103	1972
803811	N/A	N/A	130358	130377	GTTCAGAGATGTGCTATTTA	61	1973
803812	N/A	N/A	130530	130549	GCACAATATTTATCTTCAGG	44	1974
803813	N/A	N/A	130540	130559	TAATGTTGAGGCACAATATT	121	1975
803814	N/A	N/A	132624	132643	AAAGATCTGTAATTTCCCCA	59	1976
803815	N/A	N/A	134408	134427	AGCAATACAAATACAGCATA	55	1977
803816	N/A	N/A	136673	136692	GTAGGTAGACCAATGTAGAG	73	1978
803817	N/A	N/A	137059	137078	ATTAATAAAATACCTAGGAG	110	1979
803818	N/A	N/A	137783	137802	TACTAAGATTACAATGAGTT	82	1980
803819	N/A	N/A	137934	137953	TTCCTACAATCAATACTTAA	86	1981
803820	N/A	N/A	138184	138203	GAACTATGATTTATGCTCTT	47	1982
803821	N/A	N/A	138715	138734	ATTGCATCAGATTGATGTAC	82	1983
803822	N/A	N/A	139321	139340	AAAAATCCTCATTCATGGGA	66	1984
803823	N/A	N/A	139750	139769	TAAAGCATCTATGCTCCAAA	47	1985
803824	N/A	N/A	140044	140063	GCAGACCTAGAACTCCAAAA	39	1986
803825	N/A	N/A	140485	140504	AACAACGAGGAATATGTAAA	91	1987
803826	N/A	N/A	140731	140750	CAAAATAGACCAACCAGTCC	87	1988
803827	N/A	N/A	140958	140977	CATCCAAACATAAACAGAAA	85	1989
803828	N/A	N/A	141091	141110	GTTAGCCTTTTATACCTAGA	29	1990
803829	N/A	N/A	141151	141170	ATCTGTAACTTTTGAATGTT	77	1991
803830	N/A	N/A	142094	142113	GGTCTTGATCCCCACTCCTT	110	1992
803831	N/A	N/A	142406	142425	TATCAAGGAGACCTGTTGGC	114	1993
803832	N/A	N/A	142595	142614	AAGTTTTACATGAAGTCTCA	92	1994
803833	N/A	N/A	144471	144490	AGCTGTTATGGGAACCCAAA	60	1995

표 26

[0625]

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	24	222
803625	N/A	N/A	81585 87842	81604 87861	TAGTGTTTGAAGGAATAGCT	69	1787
876008	62	81	3181	3200	CGTCCGCTGCTCAGGGAACC	39	1996
876032	737	756	18636	18655	AACGCACTTAACAATATCAT	33	1997
876056	872	891	21703	21722	ATAGCTTCCACCACAATATT	71	1998
876080	1337	1356	31053	31072	TTTGATGAAGAATGCATCAG	83	1999
876104	1486	1505	35433	35452	CACTTTCAGCCACTTCAGGA	47	2000
876128	1728	1747	41961	41980	AATATCATTCTTGAAACACT	44	2001
876152	2493	2512	62114	62133	ATCCAGGGCCAGCCTCCTTA	76	2002
876176	3158	3177	73694	73713	TGAAGCTCCAGCTTTTCAAG	45	2003
876200	3571	3590	77320	77339	TCTCCACTTTAGGACAAGCC	35	2004
876224	3856	3875	82201	82220	GATGCAGTTTCTCTACTCTA	24	2005
876248	4319	4338	87223	87242	GGATGAGTACTATAGAATTC	41	2006
876272	4754	4773	92177	92196	TTCCGGTCAATTACGGGAAA	63	2007
876296	5075	5094	98223	98242	ATCTGGAATTTTTCTAGGAG	49	2008
876320	5482	5501	100471	100490	CAGGAAACCATTCTTCCATG	44	2009
876344	5833	5852	106524	106543	GTTTATTAAAAATCTTCACA	76	2010
876368	6603	6622	129748	129767	AATGCTTGCATTCCTGCTGT	70	2011
876392	7223	7242	141584	141603	TCCACAACAGGGCTATTTTG	75	2012
876416	8192	8211	146361	146380	AATTCATTTGAATATTTACA	89	2013
876440	9043	9062	147212	147231	GTTAAAGCATAGCTTCCTTT	63	2014
876464	N/A	N/A	4983	5002	AATGAAGGTGGCCAGAATCA	125	2015
876488	N/A	N/A	7242	7261	AAGTGAGTATTAAAATGTCA	112	2016
876512	N/A	N/A	9238	9257	CAAAATGTAAGTTATCAGAA	138	2017
876536	N/A	N/A	12445	12464	TCAATAATGTTTAGTTAGTT	85	2018
876560	N/A	N/A	15299	15318	ACTATAGTACATGTATCTCA	68	2019
876584	N/A	N/A	17431	17450	TTATACATGACAGCCTGAAG	121	2020
876608	N/A	N/A	19744	19763	AGAACACTTATTACATACCA	56	2021
876632	N/A	N/A	21991	22010	TTTTTGACACTCCTTTTAAA	93	2022
876656	N/A	N/A	25071	25090	ACGATCATTCCTTATTATTC	52	2023
876680	N/A	N/A	27616	27635	GGCACGACAATATTCATTGT	68	2024
876704	N/A	N/A	30008	30027	CAACCTGCTGGCTAGTCACC	40	2025
876728	N/A	N/A	32100	32119	TAATTATACAAAGCTATAAG	126	2026
876752	N/A	N/A	33547	33566	ATAGAACATTTTACACACTA	63	2027
876776	N/A	N/A	35959	35978	AACCGCCAGCTATATAATCT	73	2028
876800	N/A	N/A	38194	38213	AGGTGATAACAGATGTCAGT	104	2029
876824	N/A	N/A	39985	40004	AGTAATAGATTGAAAGAAAC	90	2030
876848	N/A	N/A	42029	42048	TTAATAGTATAAATACAGAA	119	2031

[0626]

[0627]

876872	N/A	N/A	45638	45657	CCGACTGCTGAGGTTACACC	64	2032
876896	N/A	N/A	47955	47974	GTGAGGGAGAGGACATAAAG	99	2033
876920	N/A	N/A	49786	49805	TGTATTACATAGGTATGACT	52	2034
876944	N/A	N/A	52148	52167	CTTTAAAGATGCAGAAATAA	100	2035
876968	N/A	N/A	55095	55114	TTACCCGTGCATGCACCTGT	119	2036
876992	N/A	N/A	57336	57355	ATATTAAATACAGTAAGGTT	115	2037
877016	N/A	N/A	60029	60048	CCATTCACTCCTTACTTTGT	66	2038
877040	N/A	N/A	62799	62818	AAAGATAAAAATAGTGTCAG	91	2039
877064	N/A	N/A	65735	65754	CTCAAGTTTTTCCAGATGAT	55	2040
877088	N/A	N/A	67068	67087	AGGTTTCTTAAGTGGGATAC	40	2041
877112	N/A	N/A	70290	70309	GCTTAGAGACAAATTAAGGG	37	2042
877136	N/A	N/A	72623	72642	TTATATATAAATTCGAAAGA	158	2043
877160	N/A	N/A	73942	73961	TCAGATCTGTTTCCATTGCC	31	2044
877184	N/A	N/A	75823	75842	CAATTTCTAATTTTATAATG	111	2045
877208	N/A	N/A	78402	78421	ATTTCCTCTATTATTTCATA	47	2046
877239	N/A	N/A	83094	83113	AATACAGTATACAGGCCAGT	32	2047
877263	N/A	N/A	85311	85330	CATTACCTTTCTTGATTTAT	85	2048
877287	N/A	N/A	88256	88275	TTTCCTTTCCCATCTTCATG	92	2049
877311	N/A	N/A	90591	90610	GAGGACAAAAAATGATCTCT	70	2050
877335	N/A	N/A	92465	92484	CTAAATTTGTTTTCTTATGA	129	2051
877359	N/A	N/A	94743	94762	ACCAGGGAGGCAATATAGAA	62	2052
877383	N/A	N/A	96119	96138	CCACATGGAGAAGCACCAAT	62	2053
877407	N/A	N/A	99047	99066	AAAGTCAATGAAGGTAATCA	56	2054
877431	N/A	N/A	101670	101689	ATTAAGGCAAATACAAAGAT	127	2055
877455	N/A	N/A	104228	104247	GCTGCATTAATATGGAGTAT	47	2056
877479	N/A	N/A	106092	106111	TGCCCTTCCAACTCAATCAC	82	2057
877503	N/A	N/A	108922	108941	TTATAGATAAAACTTGAAGA	126	2058
877527	N/A	N/A	111504	111523	ATGCTTTAAACTGTGATTGC	72	2059
877551	N/A	N/A	113499	113518	TTAAGATGATGGGTTCTAGA	77	2060
877575	N/A	N/A	116118	116137	TGCAAGAAACACAAGTTGGA	102	2061
877599	N/A	N/A	118373	118392	ATGCACAGGAAATCTTATTC	96	2062
877623	N/A	N/A	120463	120482	ATATTGGAGATTAAAAGGGA	121	2063
877647	N/A	N/A	122643	122662	TTTACAAACGACATAATCCT	117	2064
877671	N/A	N/A	126280	126299	AGACCCAAATAACGATTTAA	55	2065
877695	N/A	N/A	128683	128702	CCAAATCAAGAGCTCACAAC	91	2066
877719	N/A	N/A	133235	133254	TAGTACTTTTTTTCCAATAC	65	2067
877743	N/A	N/A	136955	136974	AGATATTCATGCTCACAGAC	142	2068
877767	N/A	N/A	140322	140341	TGTTGTCAGAGAGCCACTAC	71	2069
877791	N/A	N/A	141782	141801	GAAGCATTACAAATTTTTTT	105	2070
877815	N/A	N/A	144092	144111	CCAAAGTACATACAATTCAA	61	2071

표 27

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	29	222
803626	N/A	N/A	81586 87843	81605 87862	ATAGTGTTTGAAGGAATAGC	50	1788
876009	191	210	3310	3329	TTTCCTTCCTGGACATTGTT	50	2072
876033	738	757	18637	18656	TAACGCACTTAACAATATCA	31	2073
876057	874	893	21705	21724	TCATAGCTTCCACCACAATA	74	2074
876081	1342	1361	31058	31077	CTTCCTTTGATGAAGAATGC	39	2075
876105	1487	1506	35434	35453	CCACTTTCAGCCACTTCAGG	55	2076
876129	1865	1884	52779	52798	GAATCCATAGCACCTTCCAG	62	2077
876153	2532	2551	62153	62172	TATACAAAATCCTCCAAGGC	71	2078
876177	3198	3217	73734	73753	TTCACATAGCTGTTGTGGAA	76	2079
876201	3576	3595	77325	77344	GAAACTCTCCACTTTAGGAC	30	2080
876225	3857	3876	82202	82221	AGATGCAGTTTCTCTACTCT	43	81
876249	4320	4339	87224	87243	GGGATGAGTACTATAGAATT	44	2081
876273	4755	4774	92178	92197	TTTCCGGTCAATTACGGGAA	48	2082
876297	5077	5096	98225	98244	CAATCTGGAATTTTTCTAGG	67	2083
876321	5522	5541	100511	100530	AGAGTTTCTCCTTCACCACA	42	2084
876345	5875	5894	N/A	N/A	AAAGCACCACAAGCTCTTGT	18*	2085
876369	6605	6624	129750	129769	CAAATGCTTGCATTCCTGCT	61	2086
876393	7263	7282	141624	141643	TATTAGTCCACAGAGTTTTT	108	2087
876417	8267	8286	146436	146455	GAAGTTGTGTAAGATGCACT	83	2088
876441	9084	9103	147253	147272	GAGCTCTATTATATATGATT	68	2089
876465	N/A	N/A	5078	5097	TTATCTAGACCCTGCAGACC	105	2090
876489	N/A	N/A	7262	7281	GAAGGAAAAATACTACTTTT	92	2091
876513	N/A	N/A	9756	9775	AGTTTTAGAGGTTGTACCAA	62	2092
876537	N/A	N/A	12772	12791	GTAGTGGGCCGGTGGCCGTT	77	2093
876561	N/A	N/A	15455	15474	GCTTAATTGCTCTACAGTCC	48	2094
876585	N/A	N/A	17472	17491	ATCCTAATTGTCATCGAAAG	99	2095
876609	N/A	N/A	19783	19802	ATAAAATACATATTGTCTAA	97	2096
876633	N/A	N/A	22053	22072	TATAGAACTACATCTATAAA	103	2097
876657	N/A	N/A	25245	25264	TACAAGTTGCTACAATGGAG	69	2098
876681	N/A	N/A	27636	27655	ATGTCATGTCTGTGACACAC	65	2099
876705	N/A	N/A	30159	30178	TTATGATGTTTGAATGGCAC	108	2100
876729	N/A	N/A	32279	32298	ATTTTTTGCCCTCTAAAAAT	109	2101
876753	N/A	N/A	33681	33700	CCCAGCAAATGCTGCTGGTC	96	2102
876777	N/A	N/A	36087	36106	TGTGCCAATTATTTTTTTTA	84	2103
876801	N/A	N/A	38237	38256	AATACAGACATAGGTGTTTT	86	2104
876825	N/A	N/A	40148	40167	TTCTTAAAGAATTTCACATT	111	2105

[0628]

876849	N/A	N/A	42157	42176	TTTCACTTCCCACATCCCCA	91	2106
876873	N/A	N/A	45665	45684	CACAGCACTTACTTGCTCTC	45	2107
876897	N/A	N/A	48048	48067	AATTCCAGGAACCACAAACT	98	2108
876921	N/A	N/A	49975	49994	TCAGTACAGGTTAATGATGA	63	2109
876945	N/A	N/A	52174	52193	CAGCTTCATGTAATAGGTTT	44	2110
876969	N/A	N/A	55241	55260	CCTCTAATATTACATATTAA	111	2111
876993	N/A	N/A	57372	57391	AATCCATAGGCAAGTGGGAT	63	2112
877017	N/A	N/A	60530	60549	ACCATTTCTCCTCCCGGCTC	83	2113
877041	N/A	N/A	62800	62819	AAAAGATAAAAATAGTGTCA	136	2114
877065	N/A	N/A	65802	65821	TTCCTTGACCCATCACTTTA	87	2115
877089	N/A	N/A	67069	67088	AAGGTTTCTTAAGTGGGATA	60	2116
877113	N/A	N/A	70299	70318	TGGCCTTCTGCTTAGAGACA	36	2117
877137	N/A	N/A	72643	72662	ACTACTTTTTATAACTAAAT	150	2118
877161	N/A	N/A	73943	73962	ATCAGATCTGTTTCCATTGC	36	2119
877185	N/A	N/A	76014	76033	TTTGAATTAATGATTTAACA	128	2120
877209	N/A	N/A	78477	78496	GAATTCCTGTTTATTGTCAT	64	2121
877240	N/A	N/A	83109	83128	AGCTGAAAAACAAGTAATAC	112	2122
877264	N/A	N/A	85425	85444	AATTAGAGAAAAAGACTAAA	117	2123
877288	N/A	N/A	88395	88414	AAGAAAAGAACAACTGTCCT	75	2124
877312	N/A	N/A	90592	90611	AGAGGACAAAAAATGATCTC	86	2125
877336	N/A	N/A	92591	92610	ACATTATGAATGTCATTTGA	111	2126
877360	N/A	N/A	94819	94838	TCCTGATTAACATTCTTTAA	76	2127
877384	N/A	N/A	96218	96237	ATCTGCTTCATTTCTCTTGG	60	2128
877408	N/A	N/A	99066	99085	GCAAATGATTTTACTGCTTA	52	2129
877432	N/A	N/A	101696	101715	CTTATTTGCCTCCCATATCC	112	2130
877456	N/A	N/A	104260	104279	TTTTTAAAGCCCTTCTCTAT	110	2131
877480	N/A	N/A	106129	106148	CTACACTTCCAACTTTGTGT	97	2132
877504	N/A	N/A	108958	108977	GAAACCTGTAAGAGACAGTC	111	2133
877528	N/A	N/A	111524	111543	GTGTGATGTTAAATTGATTC	58	2134
877552	N/A	N/A	113529	113548	CATTTTTATAGAAGGCAGAT	68	2135
877576	N/A	N/A	116214	116233	ACTCTCCTACTAGACTGTAA	69	2136
877600	N/A	N/A	118773	118792	ATTCTCTTCTTTTTATTCAG	64	2137
877624	N/A	N/A	120519	120538	ATTAGGCCCTGGGTTTCTGA	87	2138
877648	N/A	N/A	122804	122823	AAGATAAAACATATCCCTAA	83	2139
877672	N/A	N/A	126378	126397	TTTATGTAAATTTACTTGTC	108	2140
877696	N/A	N/A	128758	128777	TAAAGTCATTATAGTTGTAC	83	2141
877720	N/A	N/A	133258	133277	AAAAAACAGGCTTCACATTT	127	2142
877744	N/A	N/A	137015	137034	ATCTCTATAAGGAAACCTGA	120	2143
877768	N/A	N/A	140412	140431	TTTAACAATCATTAGTATAT	88	2144
877792	N/A	N/A	141884	141903	GAGAACATTCTTTGTAATAC	66	2145
877816	N/A	N/A	144288	144307	TGAGAAGAACTGGATGTTCA	65	2146

표 28

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

[0629]

[0630]

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	38	222
780619	N/A	N/A	81587	81606	CATAGTGTTTGAAGGAATAG	91	669
			87844	87863			
876010	304	323	3695	3714	AGACGATCAACAGAGGCACA	56	2147
876034	740	759	18639	18658	GTTAACGCACTTAACAATAT	46	2148
876058	875	894	21706	21725	TTCATAGCTTCCACCACAAT	72	2149
876082	1403	1422	N/A	N/A	TTTCTGAAATTAACATTTTG	88	2150
876106	1489	1508	35436	35455	AGCCACTTTCAGCCACTTCA	41	2151
876130	1867	1886	52781	52800	CTGAATCCATAGCACCTTCC	55	2152
876154	2537	2556	62158	62177	TTTCCTATACAAAATCCTCC	55	2153
876178	3212	3231	N/A	N/A	AAACTCTTCAGAGTTTCACA	108	2154
876202	3615	3634	N/A	N/A	CAAGAAAGGCATAGCAGCAA	77	2155
876226	3858	3877	82203	82222	AAGATGCAGTTTCTCTACTC	105	2156
876250	4383	4402	87287	87306	TTCAGCCTGTCCCTTGCTGA	91	2157
876274	4757	4776	92180	92199	CGTTTCCGGTCAATTACGGG	32	2158
876298	5151	5170	99157	99176	GGGAAGCTCTATCACAGGCC	31	2159
876322	5543	5562	100532	100551	TATAATGCCCATTTCTTCAA	99	2160
876346	5880	5899	113077	113096	GTGGCAAAGCACCACAAGCT	35	2161
876370	6606	6625	129751	129770	CCAAATGCTTGCATTCCTGC	73	2162
876394	7324	7343	142972	142991	TTTTGTGTTTTGATTCCTTG	65	2163
876418	8308	8327	146477	146496	TTTCATTAGTACTTTTAATG	120	2164
876442	9131	9150	147300	147319	AAATTGCAAATACAAAGTAA	137	2165
876466	N/A	N/A	5103	5122	CTGGGTTGTCAAGTATAGCA	81	2166
876490	N/A	N/A	7469	7488	TATCATGTTAAATGGCATCT	56	2167
876514	N/A	N/A	9834	9853	CATATAATTTCTAAATTATG	126	2168
876538	N/A	N/A	12900	12919	GTTGATATATTAAAATATAG	101	2169
876562	N/A	N/A	15482	15501	ATTCTCATCTAGAATGCAAA	93	2170
876586	N/A	N/A	17692	17711	TACTCTACATTTATAGTCAT	117	2171
876610	N/A	N/A	19865	19884	GAAGGCTCACACCTTCAGAT	72	2172
876634	N/A	N/A	22186	22205	TATACAACATTTAAGTTGGA	95	2173
876658	N/A	N/A	25650	25669	CATCTGTGTATAAATATGTA	85	2174
			25680	25699			
			25710	25729			
			25740	25759			
			25804	25823			
			25868	25887			
876682	N/A	N/A	27649	27668	CTGATTCCCTCTCATGTCAT	63	2175
876706	N/A	N/A	30201	30220	ACTCCTTGCTACAGCTTGTA	40	2176
876730	N/A	N/A	32460	32479	GGTGAGATGAAAAAGGAGGA	64	2177
876754	N/A	N/A	33697	33716	CTGTTTATCAAGTTCCCCCA	61	2178
876778	N/A	N/A	36104	36123	GTTTTCACTGCAACTTCTGT	73	2179
876802	N/A	N/A	38252	38271	TAAATGTGTTGGATGAATAC	104	2180

876826	N/A	N/A	40280	40299	TAGAGTTTCATATCCCTTTG	58	2181
876850	N/A	N/A	42247	42266	GAGTGGATTTATGTTACTGG	35	2182
876874	N/A	N/A	45671	45690	CCACATCACAGCACTTACTT	60	2183
876898	N/A	N/A	48092	48111	CATAGTCTGTAGGTAGTAGT	54	2184
876922	N/A	N/A	50209	50228	CGTTAATAATTTTCAAACAA	145	2185
876946	N/A	N/A	52275	52294	CTTGACCAGTAAAACGCAAT	72	2186
876970	N/A	N/A	55359	55378	CAGAGTCTGTCCTCTTCACT	79	2187
876994	N/A	N/A	57490	57509	GTTTATGTGATTTTAATTCA	60	2188
877018	N/A	N/A	60774	60793	AAGCACTACAGAGCTCTGAT	75	2189
877042	N/A	N/A	63004	63023	CTGACCAAAACTGGTGTTTT	131	2190
877066	N/A	N/A	65861	65880	TTTCCTGGAATATTAACCAT	57	2191
877090	N/A	N/A	67071	67090	AAAAGGTTTCTTAAGTGGGA	70	2192
877114	N/A	N/A	70300	70319	CTGGCCTTCTGCTTAGAGAC	55	2193
877138	N/A	N/A	72664	72683	ATATAATTTCTCATTAACCA	79	2194
877162	N/A	N/A	73945	73964	TAATCAGATCTGTTTCCATT	52	2195
877186	N/A	N/A	76016	76035	TATTTGAATTAATGATTTAA	155	2196
877210	N/A	N/A	78507	78526	TATTCTCTATGAAGGAAGAT	72	2197
877241	N/A	N/A	83229	83248	GACAAACAAATTATCAATTT	70	2198
877265	N/A	N/A	86490	86509	TCTTTTACATGTCACACTAT	116	2199
877289	N/A	N/A	88459	88478	TGTTGATATTTGCTTTCCGT	45	2200
877313	N/A	N/A	90605	90624	TGAAAAATAAATGAGAGGAC	107	2201
877337	N/A	N/A	92763	92782	GAGAATTTTCATCTTTGAGA	42	2202
877361	N/A	N/A	94894	94913	TTATTTGTCCCCATACATGA	102	2203
877385	N/A	N/A	96275	96294	GTAGCAGAATTAATATTTTT	59	2204
877409	N/A	N/A	99079	99098	CCAACCTTGTTGAGCAAATG	109	2205
877433	N/A	N/A	101710	101729	CACCTGAAAACTGTCTTATT	123	2206
877457	N/A	N/A	104825	104844	ACTGGAATCAGAAATAGAAT	119	2207
877481	N/A	N/A	106421	106440	AATTAAGCTGTCCAAGCGAA	150	2208
877505	N/A	N/A	109331	109350	TGAATGTGAAGAATGCCCAT	97	2209
877529	N/A	N/A	111530	111549	TAGCTTGTGTGATGTTAAAT	56	2210
877553	N/A	N/A	113596	113615	GACTCATCTTTCCTCATTGG	52	2211
877577	N/A	N/A	116216	116235	TGACTCTCCTACTAGACTGT	66	2212
877601	N/A	N/A	118774	118793	CATTCTCTTCTTTTTATTCA	60	2213
877625	N/A	N/A	120524	120543	AAAAGATTAGGCCCTGGGTT	71	2214
877649	N/A	N/A	122888	122907	ATTATACATTTCCTTAGAAT	142	2215
877673	N/A	N/A	126380	126399	TATTTATGTAAATTTACTTG	115	2216
877697	N/A	N/A	128864	128883	ATTTTTACTGTGGACATAAA	96	2217
877721	N/A	N/A	133263	133282	GGTACAAAAAAACAGGCTTCA	55	2218
877745	N/A	N/A	137032	137051	AACAAAGATGATGAACGATC	134	2219
877769	N/A	N/A	140492	140511	ATGAATGAACAACGAGGAAT	145	2220
877793	N/A	N/A	141955	141974	TGTGACAGAACTATGTCAAA	87	2221
877817	N/A	N/A	144304	144323	AATATAGCATAGTAATTGAG	109	2222

표 29

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

[0631]

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	32	222
803627	N/A	N/A	81588	81607	CCATAGTGTTTGAAGGAATA	47	1789
			87845	87864			
876011	309	328	3700	3719	GTCCAAGACGATCAACAGAG	47	2223
876035	797	816	18696	18715	AGGGAATGTAAACAATGCAG	41	2224
876059	876	895	21707	21726	TTTCATAGCTTCCACCACAA	59	2225
876083	1408	1427	N/A	N/A	GTATTTTTCTGAAATTAACA	87	2226
876107	1490	1509	35437	35456	CAGCCACTTTCAGCCACTTC	49	2227
876131	1952	1971	52992	53011	TTCTTTGTAATCAAGTATCC	110	2228
876155	2558	2577	62179	62198	CCAAGCCAAGAAGGTTCAAC	51	2229
876179	3214	3233	N/A	N/A	TCAAACTCTTCAGAGTTTCA	97	2230
876203	3620	3639	80900	80919	GGAGGCAAGAAAGGCATAGC	46	2231
876227	3860	3879	82205	82224	GAAAGATGCAGTTTCTCTAC	59	2232
876251	4388	4407	87292	87311	TCAACTTCAGCCTGTCCCTT	105	2233
876275	4781	4800	92204	92223	TTTTCTCTCACTAGTTGTAA	48	2234
876299	5191	5210	99197	99216	TTTCATATAGTCGGATGATA	72	2235
876323	5566	5585	100555	100574	GTTCTTCACCATCATTAAAA	61	2236
876347	5979	5998	113176	113195	AAGCAGGCGATCCAAGGAAC	112	2237
876371	6645	6664	129790	129809	AAATGAGAGCTGTCCTCTGT	71	2238
876395	7354	7373	143002	143021	AGAGGGTTTTCACTCTCCCA	60	2239
876419	8313	8332	146482	146501	TGTTTTTTCATTAGTACTTT	91	2240
876443	9170	9189	147339	147358	AATATGGTATTCATTTTTTT	100	2241
876467	N/A	N/A	5161	5180	ATGCTCAGGCTTGGGCAATT	64	2242
876491	N/A	N/A	7474	7493	TGGAATATCATGTTAAATGG	65	2243
876515	N/A	N/A	10519	10538	AAATAAATACTCAAGGCCAT	88	2244
876539	N/A	N/A	13003	13022	TATTTTCACCCAACTCCATA	126	2245
876563	N/A	N/A	15487	15506	TTTGCATTCTCATCTAGAAT	108	2246
876587	N/A	N/A	17742	17761	CCCCTGAGTCCTGGAGAACC	99	2247
876611	N/A	N/A	19889	19908	ATTGGGTTTTACTCTGCCTA	41	2248
876635	N/A	N/A	22443	22462	CCACATGCAAAAATATTTCT	57	2249
876659	N/A	N/A	25651	25670	ACATCTGTGTATAAATATGT	61	2250
			25681	25700			
			25711	25730			
			25741	25760			
			25805	25824			
			25869	25888			
876683	N/A	N/A	27820	27839	GATGAATATTCAATGGCATT	36	2251
876707	N/A	N/A	30247	30266	AAAACACAAAGGCTCACGGA	73	2252
876731	N/A	N/A	32510	32529	CTGTCAGTGCCCTGGCCACT	42	2253
876755	N/A	N/A	33873	33892	GTGGCTAGCTTCTAGCCAAG	110	2254
876779	N/A	N/A	36197	36216	TGTTATTATCATTCCTCTTT	95	2255
876803	N/A	N/A	38423	38442	AAAGCCTTTTATATATGCAT	57	2256

[0632]

876827	N/A	N/A	40345	40364	CTTTTTAAGTCCTCCATATT	65	2257
876851	N/A	N/A	42335	42354	AGAAAACAGCAGCCATAGTA	113	2258
876875	N/A	N/A	45683	45702	AAGTGATTTTCTCCACATCA	62	2259
876899	N/A	N/A	48094	48113	TGCATAGTCTGTAGGTAGTA	23	2260
876923	N/A	N/A	50229	50248	TGTTGTCACCCTTGTAAAAT	85	2261
876947	N/A	N/A	52382	52401	AATTCACTGAGGGTTAGAAT	82	2262
876971	N/A	N/A	55369	55388	AGCACATCCCCAGAGTCTGT	76	2263
876995	N/A	N/A	57777	57796	TAAATTGAAAGAATAGTAGA	147	2264
877019	N/A	N/A	60820	60839	AAATGCCCACCAGTCTCCAA	93	2265
877043	N/A	N/A	63105	63124	AAACCTTGATGTATAAAGGC	115	2266
877067	N/A	N/A	65930	65949	TACACAAGCCACGAAAGGAT	72	2267
877091	N/A	N/A	67193	67212	TCTTCATTGACACACCACAC	52	2268
877115	N/A	N/A	70305	70324	TCACTCTGGCCTTCTGCTTA	76	2269
877139	N/A	N/A	72670	72689	ATATCCATATAATTTCTCAT	97	2270
877163	N/A	N/A	74025	74044	GAATTAAATGATTAAAGTAT	91	2271
877187	N/A	N/A	76071	76090	TTTTGTAAATTATTTCCAGA	80	2272
877211	N/A	N/A	78563	78582	AAAAATTATTTTACTGAGTC	158	2273
877242	N/A	N/A	83232	83251	TGAGACAAACAAATTATCAA	55	2274
877266	N/A	N/A	86571	86590	CGCTGTTGAAGAAACCTAGT	62	2275
877290	N/A	N/A	88524	88543	GAGCCTGGAGGGAAAGACAC	99	2276
877314	N/A	N/A	90620	90639	GATCAAAGGCAAATATGAAA	81	2277
877338	N/A	N/A	92815	92834	ATTTCTAGCAAGGTAATATG	82	2278
877362	N/A	N/A	94924	94943	GTACAGGATGCAGCTACCTA	56	2279
877386	N/A	N/A	96286	96305	GTTACTAGAATGTAGCAGAA	74	2280
877410	N/A	N/A	99359	99378	CATCTCCCTAATTTCTCTAA	92	2281
877434	N/A	N/A	101744	101763	GTCATTTTATAAAATATGGC	95	2282
877458	N/A	N/A	104836	104855	AACTGTTACATACTGGAATC	109	2283
877482	N/A	N/A	106589	106608	ATGTGCAATTTAATATAATT	89	2284
877506	N/A	N/A	109785	109804	ACTTGTGGCCCACAGGTCGC	87	2285
877530	N/A	N/A	111542	111561	TGTTGAAATGTATAGCTTGT	57	2286
877554	N/A	N/A	113660	113679	GACATGTGAGATGGTCATGC	55	2287
877578	N/A	N/A	116500	116519	TCTTCATAGCTTAAAGTAAA	79	2288
877602	N/A	N/A	118817	118836	GAATCTACAAATCTAACTTT	118	2289
877626	N/A	N/A	120677	120696	AAAATTGGAGGCAGAGTTTA	94	2290
877650	N/A	N/A	122924	122943	ATATTGTTACAGATACAATG	90	2291
877674	N/A	N/A	126393	126412	CTCCATAATCCTATATTTAT	83	2292
877698	N/A	N/A	128986	129005	AAGTATGTCTAAGCTTTTTA	59	2293
877722	N/A	N/A	133331	133350	TTGAAATTTTTCTTTGACCA	36	2294
877746	N/A	N/A	137262	137281	TTTCCATCTTAAATGATTAG	86	2295
877770	N/A	N/A	140513	140532	AATAGAAGAAGGCACTACAG	111	2296
877794	N/A	N/A	142230	142249	AAATAAAAATATAAAGTGGC	154	2297
877818	N/A	N/A	144312	144331	TGAGGCAAAATATAGCATAG	93	2298

표 30

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

[0633]

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	43	222
780620	N/A	N/A	81590	81609	AGCCATAGTGTTTGAAGGAA	28	670
			87847	87866			
876013	339	358	3730	3749	CTGCTGCACACTCGCGACTC	55	2299
876037	821	840	N/A	N/A	TCCACATTATTGCAAGGAAT	51	2300
876061	930	949	21761	21780	CCTATGGAGCAAACAGCAAC	89	2301
876085	1455	1474	35402	35421	CTTCTGCATTAACTCCAAAA	49	2302
876109	1493	1512	35440	35459	TTACAGCCACTTTCAGCCAC	33	2303
876133	2042	2061	53082	53101	TTAGTCTGTATTTCAGCAAC	81	2304
876157	2626	2645	65464	65483	TTCTTGCTAGTGTAGATGCT	48	2305
876181	3216	3235	N/A	N/A	TGTCAAACTCTTCAGAGTTT	40	2306
876205	3703	3722	N/A	N/A	AAGACCGCAAGTGTGGAAGA	56	2307
876229	3929	3948	83924	83943	CTGACATCCAGAGATGTCAG	89	2308
876253	4432	4451	N/A	N/A	AAGAAGCGCGAGCCTTTATA	103	2309
876277	4877	4896	93338	93357	AACTGCAGTGCTGGGTCTTG	49	2310
876301	5194	5213	99200	99219	GCATTTCATATAGTCGGATG	22	2311
876325	5610	5629	100599	100618	TTCCTCTGCTTTCTTCATCA	56	2312
876349	6023	6042	113220	113239	ATCCTGTGCTGTAGGGTTCT	58	2313
876373	6689	6708	N/A	N/A	TCAGCAACTTCCTCAGAAGT	97	2314
876397	7400	7419	143048	143067	TGGCCTCCTCCAGTTCCTAT	73	2315
876421	8402	8421	146571	146590	CTATTATGTCTAGGAAAGAC	138	2316
876445	N/A	N/A	3487	3506	CTCCTTAAGAGTCCGGGTTT	103	2317
876469	N/A	N/A	5188	5207	TGACACTCATAACTACTCCG	68	2318
876493	N/A	N/A	7785	7804	AATACAATTAAATTGGTAGT	97	2319
876517	N/A	N/A	10746	10765	AAAATCTACAACTTAACCAG	107	2320
876541	N/A	N/A	13064	13083	AAAAAGTTAAAAGCACTACT	90	2321
876565	N/A	N/A	15570	15589	CTTTAAGAATATCTCCTACA	97	2322
876589	N/A	N/A	17908	17927	AGTGATCAACATTCATTTTT	58	2323
876613	N/A	N/A	19993	20012	TTATTGTTCAGCCCCACCCA	92	2324
876637	N/A	N/A	22715	22734	CTATCCTGTGAACAATATTG	74	2325
876661	N/A	N/A	25662	25681	TATATTTATATACATCTGTG	60	2326
			25692	25711			
			25722	25741			
			25752	25771			
			25816	25835			
			25880	25899			
876685	N/A	N/A	27910	27929	AGTTAAGTGAAACATTAGCT	98	2327
876709	N/A	N/A	30373	30392	AACAAATAGACGGTCAAGAT	58	2328
876733	N/A	N/A	32619	32638	TCCCTGTCCAGACCTCTTTA	83	2329
876757	N/A	N/A	33996	34015	ATACTGCCAGAGCCTGAAAA	81	2330
876781	N/A	N/A	36419	36438	TTAGTTAGACTGATGTTAAA	96	2331
876805	N/A	N/A	38456	38475	GAAGAAATTATTTGTGCCTC	56	2332

[0634]

876829	N/A	N/A	40740	40759	GAGGTCCTACTATTCAAATG	49	2333
876853	N/A	N/A	42906	42925	CTTCTCTTTTTCATACTCAG	47	2334
876877	N/A	N/A	46382	46401	AGAAGACTGGTTTTACTTTA	78	2335
876901	N/A	N/A	48096	48115	GGTGCATAGTCTGTAGGTAG	28	2336
876925	N/A	N/A	50288	50307	TTCACAGGTGTGTATTTCAC	62	2337
876949	N/A	N/A	52569	52588	AAATCAGTATCCTTGATTTT	92	2338
876973	N/A	N/A	55733	55752	GGAAAAAGAACTAATACCCT	97	2339
876997	N/A	N/A	57805	57824	AAAATCCTGTTGGGTAGAAA	84	2340
877021	N/A	N/A	61061	61080	CCCTTACAGCTAGCAAGCAA	75	2341
877045	N/A	N/A	63132	63151	AACTTTTGGAGCCTACTGAG	79	2342
877069	N/A	N/A	66149	66168	TCATTATATATTTCACCATA	47	2343
877093	N/A	N/A	67368	67387	TAAGAATAAGGTATAAATCA	114	2344
877117	N/A	N/A	70856	70875	ATTTTAAATTCCCCTACTCT	87	2345
877141	N/A	N/A	72684	72703	TGAGTGAAAAAGCTATATCC	52	2346
877165	N/A	N/A	74316	74335	AGAGCTATCCTATCAACAAA	83	2347
877189	N/A	N/A	76262	76281	CTTACACACCTCTGGTAACT	47	2348
877213	N/A	N/A	78841	78860	TTTGTCTGTGCTCTGAACTT	69	2349
877244	N/A	N/A	83428	83447	CCTAATTGGAGTAATTTCTT	89	2350
877268	N/A	N/A	86896	86915	TCCATACAGTCTACCAGGTT	50	2351
877292	N/A	N/A	89032	89051	GGCATCAAAAACATTTTCTC	23	2352
877316	N/A	N/A	90814	90833	AGATGCCTGCTCTGCTAATG	83	2353
877340	N/A	N/A	93050	93069	TTCACACATAAGTAGAAATT	106	2354
877364	N/A	N/A	95117	95136	CTGTATAAGATATACCCATC	35	2355
877388	N/A	N/A	96349	96368	TGCTATTCATATAGAGTCTC	27	2356
877412	N/A	N/A	99735	99754	ATTTTGGAAACCAGTAACAC	94	2357
877436	N/A	N/A	101885	101904	TTTGAGTATGTCACCATGTA	59	2358
877460	N/A	N/A	104875	104894	ATTAGTTAGGATTGTTGGTA	62	2359
877484	N/A	N/A	106759	106778	AGGATTCTCAGATACAGTGT	99	2360
877508	N/A	N/A	109926	109945	AATCCTATGGTGAGTACCTC	94	2361
877532	N/A	N/A	111674	111693	GATCCAATGGCAACAACCCT	97	2362
877556	N/A	N/A	113970	113989	GGAATGTAAGGTGACTCTCA	80	2363
877580	N/A	N/A	116687	116706	AGACTAGCAAAATAGCTTTT	97	2364
877604	N/A	N/A	118908	118927	GTGGACCTGAATTTGATTTG	58	2365
877628	N/A	N/A	120831	120850	AGGAAGATTCATTAAACGGA	76	2366
877652	N/A	N/A	123128	123147	AAAGATGGAGCTCAGCAGTC	89	2367
877676	N/A	N/A	126731	126750	TTTGCCTTATAACTATTTTT	92	2368
877700	N/A	N/A	129195	129214	ATTCTGTTTTTGATCTGGAG	78	2369
877724	N/A	N/A	133350	133369	CCTTGCCCAATTCCATCCAT	49	2370
877748	N/A	N/A	138041	138060	TATTCTTGTTTGAAACTGGT	46	2371
877772	N/A	N/A	140642	140661	CCCTCACACTAGATTATGAG	72	2372
877796	N/A	N/A	142347	142366	AGAAAAACTGTCAGATGAAT	116	2373
877820	N/A	N/A	144537	144556	ATATTCTAGTGAAGAGACTA	164	2374

표 31

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

[0635]

[0636]

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	19	222
780621	N/A	N/A	81593 87850	81612 87869	AAAAGCCATAGTGTTTGAAG	35	671
876016	395	414	10419	10438	CTTTGCATTGTACCTGGACA	37	2375
876040	825	844	N/A	N/A	GACTTCCACATTATTGCAAG	36	2376
876064	1070	1089	N/A	N/A	ATAGTCTCAGTGAGGAGGGC	50	2377
876088	1468	1487	35415	35434	GAGAATGTATATGCTTCTGC	15	2378
876112	1539	1558	37588	37607	TATATCCAGGGAAGTGTTGC	71	2379
876136	2091	2110	56025	56044	AGAAAAAGATGCTGACAATT	86	2380
876160	2802	2821	N/A	N/A	GCCTTCACTTCCTTCACTAT	59	2381
876184	3223	3242	76357	76376	CCAAATGTGTCAAACTCTTC	39	2382
876208	3791	3810	82136	82155	TTATGGCTAAATAAGAGTTC	69	2383
876232	4012	4031	84007	84026	GATGCAGTTCATCCAAAGGA	35	2384
876256	4609	4628	88710	88729	TTTTCCGAAGTTTTGCCAAA	73	2385
876280	4967	4986	98115	98134	GGGTGTTTTGGACAACCTTC	37	2386
876304	5198	5217	99204	99223	TAAGGCATTTCATATAGTCG	48	2387
876328	5647	5666	101285	101304	TGAGCCTTGGTTGATCTGGA	21	2388
876352	6072	6091	118405	118424	AATCATGGCTGAGTGGAGGT	80	2389
876376	6738	6757	132448	132467	TTCCTTTTCAACAGGAAGAT	68	2390
876400	7495	7514	N/A	N/A	TTCCTAGCTGTGCTGTCATC	91	2391
876424	8539	8558	146708	146727	GAAGCAGATTAGAAAACAAG	86	2392
876448	N/A	N/A	3736	3755	CTTTACCTGCTGCACACTCG	63	2393
876472	N/A	N/A	5572	5591	CCAGAGACTGGAAATGAAAG	95	2394
876496	N/A	N/A	7851	7870	TCCATTAATCTATTCAATTA	78	2395
876520	N/A	N/A	10808	10827	GTATCGATTCTATTATTAAA	71	2396
876544	N/A	N/A	13929	13948	AATCAAGCTACCCTAATCCT	95	2397
876568	N/A	N/A	15860	15879	TAAATGAGATAAACTCCCAG	96	2398
876592	N/A	N/A	18000	18019	TATTGGGCAACAACCTGAAA	95	2399
876616	N/A	N/A	20210	20229	TTTTAGCTGCTACTTTCTTG	84	2400
876640	N/A	N/A	23220	23239	GATACATAAAAAAGAGTAAA	135	2401
876664	N/A	N/A	26207	26226	AGATTAAAACATTATCAGAT	84	2402
876688	N/A	N/A	28199	28218	ACAACTGTTAGTTTCCTTGA	55	2403
876712	N/A	N/A	30796	30815	TTTCAAAAGCATATGCAGCA	51	2404
876736	N/A	N/A	32794	32813	CAGTCGAAATTTCACAAAGT	66	2405
876760	N/A	N/A	34084	34103	CTTAAGTACTGCTTTTAAAA	69	2406
876784	N/A	N/A	36835	36854	CCTCCCCTCCTTGGGTAACC	93	2407
876808	N/A	N/A	38630	38649	TCAGCCTTTCCTTCCACACT	74	2408
876832	N/A	N/A	40891	40910	TATTACACCTTAAGAAGATG	106	2409
876856	N/A	N/A	42932	42951	TTACACAATTTAAATGTAAT	104	2410
876880	N/A	N/A	46724	46743	TTAGTTCCAGAAAATACTAT	71	2411
876904	N/A	N/A	48100	48119	CCAGGGTGCATAGTCTGTAG	44	2412
876928	N/A	N/A	50374	50393	CTTCTACAAAAAAAAGTCAG	87	2413

876952	N/A	N/A	52953	52972	CACTGAATTTCTAGGAAAAT	117	2414
876976	N/A	N/A	56393	56412	AGAATACTGAGCAAAGACAA	88	2415
877000	N/A	N/A	58100	58119	GTCTAACACAACTCCACCCT	95	2416
877024	N/A	N/A	61215	61234	CCAAGATAACAGGTAATAGA	60	2417
877048	N/A	N/A	63290	63309	CTTCCAGACTGGTGATAGCA	97	2418
877072	N/A	N/A	66302	66321	AGACACAATATTTTGGAACA	53	2419
877096	N/A	N/A	67753	67772	GTTAGAAATTTTAAAAGACT	86	2420
877120	N/A	N/A	71190	71209	CTGGAATAGGGTCTAGCAGC	37	2421
877144	N/A	N/A	72946	72965	AAAAATGGGCCCCTATTAAA	102	2422
877168	N/A	N/A	74838	74857	TCCCTTAAATATACTTAAAA	101	2423
877192	N/A	N/A	76677	76696	GTTGTTAAAACTCATTGCTA	38	2424
877216	N/A	N/A	79254	79273	GACCACTTCTCAAACTATTA	64	2425
877247	N/A	N/A	83670	83689	CTCCCAAACAATCTATGTCA	41	2426
877271	N/A	N/A	87005	87024	AACCGATCAAAGTACCTAGC	36	2427
877295	N/A	N/A	89220	89239	CACAGTGACAAAATTCATGA	50	2428
877319	N/A	N/A	91037	91056	TATCTCTTAACCCAGAGAAT	79	2429
877343	N/A	N/A	93174	93193	CTGGGACTAGAAGCTGTGCA	37	2430
877367	N/A	N/A	95220	95239	ACTTAATTACTCCACAGAAT	91	2431
877391	N/A	N/A	96751	96770	TTCTCTCATTTGAATATCAG	63	2432
877415	N/A	N/A	99949	99968	TAAAAAGAGTTAAATCCCCT	88	2433
877439	N/A	N/A	102322	102341	TGTACAAAGTATATCTTTTT	45	2434
877463	N/A	N/A	104975	104994	ATTAGATTGTAAATATGTTA	147	2435
877487	N/A	N/A	106908	106927	CCAAGTTTCTACATTTCTAA	64	2436
877511	N/A	N/A	110185	110204	TTGTTGAGAAAAGCACAGAT	94	2437
877535	N/A	N/A	111992	112011	CATTGGCATTCATTCAATCC	73	2438
877559	N/A	N/A	114281	114300	GGTATCTGCAAGGAACCTCA	87	2439
877583	N/A	N/A	117201	117220	TTCAATTGTATGAGGGCCTG	102	2440
877607	N/A	N/A	119250	119269	TTACTTCCTGCTCAAACTGA	99	2441
877631	N/A	N/A	121200	121219	CAGGAGCTCTGCTCTCAGGC	67	2442
877655	N/A	N/A	123752	123771	GTACTACTCTTTCTTTCTTT	62	2443
877679	N/A	N/A	126891	126910	TTTTTTCTGATTTGATTTGT	81	2444
877703	N/A	N/A	129329	129348	GCATGCAATTCTATATTGCA	100	2445
877727	N/A	N/A	133490	133509	CCCACTTCCTTCCAACAAGG	77	2446
877751	N/A	N/A	138235	138254	GAAAGGTTATTGCCCAAGTT	45	2447
877775	N/A	N/A	140814	140833	GCCACATCAGCATGGCAAAC	50	2448
877799	N/A	N/A	142668	142687	TACCAAAGCTATCTAATTCA	99	2449
877823	N/A	N/A	144798	144817	TTAAACGAGGTAATGTGTGT	60	2450

표 32

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시	서열 번호: 1 중단	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호

[0637]

	부위	부위					
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	37	222
803631	N/A	N/A	81594 87851	81613 87870	AAAAAGCCATAGTGTTTGAA	80	1793
876017	400	419	10424	10443	TTAAGCTTTGCATTGTACCT	40	2451
876041	827	846	N/A	N/A	AGGACTTCCACATTATTGCA	37	2452
876065	1084	1103	29345	29364	CTTGATTTAAGAAAATAGTC	83	2453
876089	1469	1488	35416	35435	GGAGAATGTATATGCTTCTG	27	2454
876113	1555	1574	37604	37623	GGACCACTGCTGCCATTATA	43	2455
876137	2130	2149	56064	56083	GAATATTACTAAGTCAAATG	84	2456
876161	2843	2862	71686	71705	CCTACACTAATTGAATTAGA	52	2457
876185	3224	3243	76358	76377	TCCAAATGTGTCAAACTCTT	31	2458
876209	3796	3815	82141	82160	TCTGATTATGGCTAAATAAG	41	2459
876233	4017	4036	84012	84031	GTTAAGATGCAGTTCATCCA	55	2460
876257	4621	4640	88722	88741	CGTTTATGATGGTTTTCCGA	79	2461
876281	5042	5061	98190	98209	GACATGTAGTTCTTTGGAAA	44	2462
876305	5199	5218	99205	99224	ATAAGGCATTTCATATAGTC	74	2463
876329	5648	5667	101286	101305	GTGAGCCTTGGTTGATCTGG	55	2464
876353	6093	6112	118426	118445	GGGTTTCAGGTCTCGGTATA	72	2465
876377	6777	6796	132487	132506	CAGGAGAGTACCAGACTGTG	71	2466
876401	7516	7535	145119	145138	CCAGCATGACATTTTTAAGG	37	2467
876425	8551	8570	146720	146739	AAGCATTAGAATGAAGCAGA	56	2468
876449	N/A	N/A	3738	3757	GCCTTTACCTGCTGCACACT	69	2469
876473	N/A	N/A	5806	5825	CTCTAAATTAATTACTTAAC	97	2470
876497	N/A	N/A	7895	7914	TGATTAAATAGAATCTCTGG	89	2471
876521	N/A	N/A	10905	10924	AAATGTACTATTTAAAGACA	84	2472
876545	N/A	N/A	13978	13997	GGCTGTCCCATCACTAGGTC	40	2473
876569	N/A	N/A	15888	15907	GTTAGACTTATCAAGCTCTA	41	2474
876593	N/A	N/A	18037	18056	TTTGATCAAGCCAGTAAGTT	47	2475
876617	N/A	N/A	20433	20452	TGTTTAAAAAAAAGGCTGTTT	88	2476
876641	N/A	N/A	23260	23279	ATTATCTTAGGGAAAGGACA	83	2477
876665	N/A	N/A	26250	26269	TGTGCTACTCTGACACCTGG	41	2478
876689	N/A	N/A	28210	28229	GTATATTTGTCACAACTGTT	52	2479
876713	N/A	N/A	30800	30819	GCTTTTTCAAAAGCATATGC	35	2480
876737	N/A	N/A	32826	32845	TGTAACCAGTCCTCAGACAC	73	2481
876761	N/A	N/A	34100	34119	ACATAAAAAGTTTTAACTTA	105	2482
876785	N/A	N/A	36869	36888	AAAGTCCCAGTTTAAACACA	73	2483
876809	N/A	N/A	38643	38662	TTTTCTTTGGGCCTCAGCCT	110	2484
876833	N/A	N/A	40900	40919	GAGGCTGCCTATTACACCTT	60	2485
876857	N/A	N/A	42939	42958	TTTTGCATTACACAATTTAA	74	2486
876881	N/A	N/A	46818	46837	TGGAGTTAGGCCATATGAAT	45	2487
876905	N/A	N/A	48102	48121	GTCCAGGGTGCATAGTCTGT	28	2488
876929	N/A	N/A	50419	50438	TACCAGTATCTTAAATTCAG	93	2489
876953	N/A	N/A	53117	53136	AGTTCCCAAATTCTTTCCAA	86	2490
876977	N/A	N/A	56418	56437	AATGGCAGGGCTCTTACATT	45	2491

[0638]

877001	N/A	N/A	58449	58468	GAGCCACCCTGCATGAAGCT	74	2492
877025	N/A	N/A	61291	61310	GCACTGCATGCTGGCCCTAC	122	2493
877049	N/A	N/A	63355	63374	TTATATAATGTGGTGAATGG	124	2494
877073	N/A	N/A	66309	66328	TGACTTGAGACACAATATTT	52	2495
877097	N/A	N/A	67953	67972	ATTGTGAACAAAGAAAATCC	110	2496
877121	N/A	N/A	71306	71325	CAAATCAATCAACGGTTACA	60	2497
877145	N/A	N/A	73081	73100	TAATTGGAGGAAATTCAACC	113	2498
877169	N/A	N/A	74847	74866	GAAAAAACATCCCTTAAATA	119	2499
877193	N/A	N/A	77052	77071	TAAAAGTTGTAATATTCATT	88	2500
877217	N/A	N/A	79613	79632	TTCAGAGTCTTGAGTTTCAT	51	2501
877248	N/A	N/A	84372	84391	TCTTTAGATTGTGTAATTGG	43	2502
877272	N/A	N/A	87027	87046	CACTTTTAGCATATTTGTCA	80	2503
877296	N/A	N/A	89765	89784	AAATGGAACAGAACTAAGCT	100	2504
877320	N/A	N/A	91067	91086	CAAATGGTTACTCAAGAGAC	68	2505
877344	N/A	N/A	93198	93217	ATTTCAGCATAGCTAGTGAC	102	2506
877368	N/A	N/A	95236	95255	CTTTCATGGAGTTTCAACTT	100	2507
877392	N/A	N/A	96941	96960	TCCCATGTTGTGTACTTTAT	36	2508
877416	N/A	N/A	100066	100085	TGCACACAACACAAGTGATT	64	2509
877440	N/A	N/A	102409	102428	TCTCCATTCCACAACATATA	98	2510
877464	N/A	N/A	105094	105113	ATGGAAAGCCTCTACCTATT	111	2511
877488	N/A	N/A	106972	106991	TGGAGGCAGCTAGGAGTCTG	100	2512
877512	N/A	N/A	110233	110252	CAAAGGCCTAAAGCCAATTA	128	2513
877536	N/A	N/A	112047	112066	AGGCCTTCCAGACCTTCTCG	108	2514
877560	N/A	N/A	114295	114314	GATATAAAGCCTCTGGTATC	98	2515
877584	N/A	N/A	117209	117228	CCTGAACTTTCAATTGTATG	73	2516
877608	N/A	N/A	119259	119278	CTAAATGATTTACTTCCTGC	77	2517
877632	N/A	N/A	121414	121433	TGCCATAGGACCCAGAATTA	146	2518
877656	N/A	N/A	124006	124025	CAGAAAGTTATCAAATATGT	90	2519
877680	N/A	N/A	126954	126973	AGCTCGAAAAAGAAATTGCA	80	2520
877704	N/A	N/A	129393	129412	TAACTTGAAAAGAAAATCTC	105	2521
877728	N/A	N/A	133512	133531	CCTAATCACATTGACAACTG	101	2522
877752	N/A	N/A	138252	138271	GAGATGACTGAAGATGTGAA	73	2523
877776	N/A	N/A	140877	140896	TTTCCCTTTCAACCTAAGAC	99	2524
877800	N/A	N/A	142754	142773	CTTTACTTGAAGCATAAATT	93	2525
877824	N/A	N/A	144813	144832	CCCAAAGTTACAATGTTAAA	72	2526

표 33

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	38	222

[0639]

780622	N/A	N/A	81596 87853	81615 87872	CTAAAAAGCCATAGTGTTTG	53	672
876019	486	505	13752	13771	ACTGGCATTATGAACTGTTA	37	2527
876043	829	848	21660	21679	TGAGGACTTCCACATTATTG	47	2528
876067	1156	1175	29417	29436	CTTCCAGCCAAAACAATTTA	99	2529
876091	1472	1491	35419	35438	TCAGGAGAATGTATATGCTT	47	2530
876115	1613	1632	37662	37681	GCCTCCAGCTGCACTGGTAA	58	2531
876139	2223	2242	56231	56250	GTAATCATCCATAGCTACTT	31	2532
876163	2867	2886	71710	71729	AATACGGCATCTCGGTAAAA	77	2533
876187	3227	3246	76361	76380	AAGTCCAAATGTGTCAAACT	44	2534
876211	3799	3818	82144	82163	TGATCTGATTATGGCTAAAT	49	2535
876235	4053	4072	84048	84067	GTCTTTGGCTTTACATCCTA	48	2536
876259	4697	4716	92120	92139	TTTTCAAGTTCTACATAGCA	59	2537
876283	5045	5064	98193	98212	TGTGACATGTAGTTCTTTGG	38	2538
876307	5251	5270	99257	99276	GTGAAATCTCAAGTAATCGA	74	2539
876331	5651	5670	101289	101308	ATGGTGAGCCTTGGTTGATC	57	2540
876355	6160	6179	118493	118512	TGCCGTAGTCAGCAATCTTT	86	2541
876379	6821	6840	132531	132550	TTTTCTAGGGTATGTCTCTT	88	2542
876403	7579	7598	N/A	N/A	AGCAAGATTGTATCTCTTTC	78	2543
876427	8599	8618	146768	146787	AATGATGTAGGATCTGCAGC	65	2544
876451	N/A	N/A	3760	3779	AATGAGTTGAAGTGAAAACA	130	2545
876475	N/A	N/A	6080	6099	TATCAACAGATTAACAAAGA	111	2546
876499	N/A	N/A	7975	7994	TTGGTGAAGCAACAGTATCA	42	2547
876523	N/A	N/A	10994	11013	TACAGATGTGCTGAAAGTTA	112	2548
876547	N/A	N/A	14093	14112	TAAAACCAATGTATTGAATG	84	2549
876571	N/A	N/A	16270	16289	ATAACTGTGTTCTACTTTTC	82	2550
876595	N/A	N/A	18575	18594	AGACTTAAAAATGAAAGACA	106	2551
876619	N/A	N/A	20584	20603	AAAATATAAGTCTTAGGGAC	89	2552
876643	N/A	N/A	23603	23622	GTGCCTAAAAAAGAATGTAT	49	2553
876667	N/A	N/A	26400	26419	AGTAGCATTTCCCTGATCAC	49	2554
876691	N/A	N/A	29101	29120	AAAAAAAAACCTAATAGACG	118	2555
876715	N/A	N/A	30926	30945	AAATATCTCTAACAACAATT	88	2556
876739	N/A	N/A	33082	33101	GTAGCCATTTTTTCTAAAAA	51	2557
876763	N/A	N/A	34583	34602	TAATGATTAAGGAATAATTT	124	2558
876787	N/A	N/A	36936	36955	ATCAGAACCATGTTCTCACT	95	2559
876811	N/A	N/A	38784	38803	CTATCATCCTCTGCACCACA	96	2560
876835	N/A	N/A	41037	41056	CCCTCCTCCAACTTTCAGTC	89	2561
876859	N/A	N/A	43022	43041	TATGTCTTTATTCTTAACAT	67	2562
876883	N/A	N/A	47044	47063	TATTCAGCTTTCTTTGCTTT	93	2563
876907	N/A	N/A	48276	48295	GATACTTTTAAATCTAATAG	116	2564
876931	N/A	N/A	50755	50774	CTTCTTTTACCTCCAAACCC	81	2565
876955	N/A	N/A	53306	53325	AATGGTGAATAACCATGCTG	76	2566
876979	N/A	N/A	56534	56553	CCTAAAGGACCCTATTACTT	99	2567
877003	N/A	N/A	59266	59285	CAGTGCCCAGGTGGTAATGA	73	2568
877027	N/A	N/A	61418	61437	TCTCTCAGTCTTCAACCTTC	93	2569
877051	N/A	N/A	63467	63486	ATGTGCAAAACACTAGTATC	74	2570
877075	N/A	N/A	66552	66571	ATTGTCAGGAAGCAAATGAT	60	2571
877099	N/A	N/A	68281	68300	TGAAAAATATGAATACCTCA	100	2572

[0640]

877123	N/A	N/A	71767	71786	ACAATTTAACTTACCAAGGA	152	2573
877147	N/A	N/A	73109	73128	GATGAAACTGGCACCAAGAA	100	2574
877171	N/A	N/A	74897	74916	GTGGGTCACCTTTCTTTCTT	43	2575
877195	N/A	N/A	77106	77125	ATCAAAGAGGACTCATTAAT	116	2576
877219	N/A	N/A	79825	79844	CAAATCTACCGTTTCTAGGA	84	2577
877250	N/A	N/A	84428	84447	GTTAACTAGTTGCTATATGA	54	2578
877274	N/A	N/A	87487	87506	ACTCGGAAAGTTTCCCAATT	63	2579
877298	N/A	N/A	89963	89982	GAATAGGAAAGTCTACAAAT	72	2580
877322	N/A	N/A	91301	91320	TAATATCCAGAGTGCCGTTA	52	2581
877346	N/A	N/A	93489	93508	CTTAACTAAACCCAAATTCT	116	2582
877370	N/A	N/A	95491	95510	TCAGACAAGTTGCTCTTGGT	31	2583
877394	N/A	N/A	97213	97232	AAGAGGTTTGTATTTAATTT	68	2584
877418	N/A	N/A	100658	100677	CACTTCATAAGTATTGAAGG	53	2585
877442	N/A	N/A	102464	102483	AATAGTTCTCACCACATAAA	101	2586
877466	N/A	N/A	105201	105220	TCTCATATAGTGCCTTGAAA	65	2587
877490	N/A	N/A	107094	107113	AGTCATGTTCAATAAAAATA	124	2588
877514	N/A	N/A	110289	110308	AGGTGGGAATATTCTAAGTA	48	2589
877538	N/A	N/A	112191	112210	CTACAAAAGTTTACCGAGGA	67	2590
877562	N/A	N/A	114372	114391	GAAAGATTCAGATAATCCTT	130	2591
877586	N/A	N/A	117360	117379	ATAATTTCTCACAAGACTTA	85	2592
877610	N/A	N/A	119341	119360	GTAATTTTACTTACAAATAA	101	2593
877634	N/A	N/A	121663	121682	TAAGAGAAATTTATGAATTA	108	2594
877658	N/A	N/A	124138	124157	AACCTAAAGACATCCAATCA	86	2595
877682	N/A	N/A	127082	127101	CAACAGGACCAAATAGGAAT	78	2596
877706	N/A	N/A	130011	130030	GGGACCCTGAGCTAAGACAT	99	2597
877730	N/A	N/A	134153	134172	AAATGGCCTTAATGTTCTCC	71	2598
877754	N/A	N/A	138408	138427	TTTGTGACTCAAAGCTAATA	76	2599
877778	N/A	N/A	140926	140945	CCATTTTCCCCTTTTAAACA	79	2600
877802	N/A	N/A	143250	143269	AAGACCATCCATATGACACT	89	2601
877826	N/A	N/A	144863	144882	AACAGCTTAACCTTTCTATA	88	2602

표 34

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	44	222
876020	528	547	13794	13813	GAGGAGATCTAAGGTCTTCA	37	2603
876044	830	849	21661	21680	ATGAGGACTTCCACATTATT	110	2604
876068	1161	1180	29422	29441	ACAGGCTTCCAGCCAAAACA	15	2605
876092	1473	1492	35420	35439	TTCAGGAGAATGTATATGCT	93	2606
876116	1637	1656	37686	37705	ATAAAATGTAAAATAGCTCG	56	2607

[0641]

876140	2262	2281	56270	56289	ATTCTGATCACACGCTCTCT	46	2608
876164	2869	2888	71712	71731	GTAATACGGCATCTCGGTAA	84	2609
876188	3228	3247	76362	76381	CAAGTCCAAATGTGTCAAAC	97	2610
876212	3800	3819	82145	82164	CTGATCTGATTATGGCTAAA	66	2611
876236	4144	4163	86639	86658	TTTTACCACTCCCAGTATTT	76	2612
876260	4725	4744	92148	92167	CACATTTTTACGCTCCGATA	49	2613
876284	5046	5065	98194	98213	CTGTGACATGTAGTTCTTTG	65	2614
876308	5338	5357	100190	100209	CTTCAGGAGACCAATTTAAG	75	2615
876332	5652	5671	101290	101309	AATGGTGAGCCTTGGTTGAT	126	2616
876356	6204	6223	118537	118556	GCCCTCTGATGTTTTTATCC	31	2617
876380	6826	6845	132536	132555	TCATCTTTTCTAGGGTATGT	38	2618
876404	7660	7679	145829	145848	TTTCAGCTAATTCTTTTCTC	100	2619
876428	8683	8702	146852	146871	GAAAAGTGTTAGATATTTAT	34	2620
876452	N/A	N/A	3761	3780	GAATGAGTTGAAGTGAAAAC	53	2621
876476	N/A	N/A	6208	6227	ATCCAGTAATCTCATCGCTG	50	2622
876500	N/A	N/A	8095	8114	ATTCTGAACAGCTTCTGGTG	102	2623
876524	N/A	N/A	11128	11147	TTTTCCTGGAAACACATTCT	71	2624
876548	N/A	N/A	14203	14222	AAGGGCAGGAATGACCACTA	127	2625
876572	N/A	N/A	16432	16451	GCAATTGAAGAAAGTCTACT	81	2626
876596	N/A	N/A	18903	18922	GTTTCTCCAGCACCAAGCCC	126	2627
876620	N/A	N/A	20690	20709	TTCCAGAAGGGCAACCAATG	89	2628
876644	N/A	N/A	23667	23686	GAACTGGACAAGTTAATCCT	57	2629
876668	N/A	N/A	26426	26445	TGCTGTTCTAGACAATTTGG	73	2630
876692	N/A	N/A	29204	29223	AAGCCTTGGTCAATTATAAA	131	2631
876716	N/A	N/A	30940	30959	CACTTGCCATTATCAAATAT	100	2632
876740	N/A	N/A	33139	33158	TGTATGCAACCTTGGGACCT	56	2633
876764	N/A	N/A	34714	34733	TGGAAAGCATTTACATAGAA	97	2634
876788	N/A	N/A	36957	36976	TGTTAACTGAAACTTGTGCA	44	2635
876812	N/A	N/A	38785	38804	TCTATCATCCTCTGCACCAC	52	2636
876836	N/A	N/A	41061	41080	TAAGGAAGGCAGCCTTGATA	42	2637
876860	N/A	N/A	43045	43064	TTTATAAAAATGTTCACACT	31	2638
876884	N/A	N/A	47090	47109	AATCTCATCCATCTGTAATT	80	2639
876908	N/A	N/A	48315	48334	TACTCTGATTTCCTCATCTT	66	2640
876932	N/A	N/A	50766	50785	CTTTACAATGTCTTCTTTTA	103	2641
876956	N/A	N/A	53309	53328	ATAAATGGTGAATAACCATG	140	2642
876980	N/A	N/A	56543	56562	TGGATAACACCTAAAGGACC	39	2643
877004	N/A	N/A	59276	59295	GTATTTGGAGCAGTGCCCAG	52	2644
877028	N/A	N/A	61596	61615	GTACCTTAACACAGTAAATA	104	2645
877052	N/A	N/A	63476	63495	TAATCTACTATGTGCAAAAC	53	2646
877076	N/A	N/A	66557	66576	TCTACATTGTCAGGAAGCAA	51	2647
877100	N/A	N/A	68445	68464	ATCTCTCACAGATGCAAAAT	74	2648
877124	N/A	N/A	71781	71800	ATAATCACAATTGCACAATT	107	2649
877148	N/A	N/A	73144	73163	GAATCATTAGGTAAATATAT	107	2650
877172	N/A	N/A	74948	74967	AGTGGAGAAGAGAGAAAGAC	63	2651
877196	N/A	N/A	77137	77156	TATCAAAAACAATTTGCTTT	143	2652
877220	N/A	N/A	79895	79914	ACAGTCTCTTTTCTTATCTG	74	2653
877232	N/A	N/A	81609	81628	TTTAGTGTCAATTCTAAAAA	101	2654
877251	N/A	N/A	84464	84483	CAGTAGCTATAATGCTTTAA	66	2655

[0642]

877275	N/A	N/A	87627	87646	TTTAGATTTCATTTAAGAAA	69	2656
877299	N/A	N/A	89982	90001	AATTACATGTCCAACAAGAG	35	2657
877323	N/A	N/A	91362	91381	AATAAAAGTATCTTCCAAAC	76	2658
877347	N/A	N/A	93509	93528	AAATTCACAAAAGTTTCTGC	90	2659
877371	N/A	N/A	95698	95717	TTTCATATCTCTTTTATCAT	77	2660
877395	N/A	N/A	97239	97258	TTTTGCTTTGTCAAATTCAC	41	2661
877419	N/A	N/A	100725	100744	CTATAATTGAATATACTATT	33	2662
877443	N/A	N/A	102592	102611	ATTAAATCAATCTAATGCAT	122	2663
877467	N/A	N/A	105313	105332	CTCAATCCCCAAGGAGTTTG	61	2664
877491	N/A	N/A	107115	107134	CTTTCACCCTGAACACACAG	72	2665
877515	N/A	N/A	110361	110380	CTCAACCCTCACCCATGCAG	100	2666
877539	N/A	N/A	112217	112236	CCTGCTTATAATCTCTGGTT	57	2667
877563	N/A	N/A	114595	114614	TCTGAAGGCTTACTATTTTA	72	2668
877587	N/A	N/A	117410	117429	ACTACAGCATTTCATGTGAT	51	2669
877611	N/A	N/A	119355	119374	ATGTATAGCCACCTGTAATT	47	2670
877635	N/A	N/A	121814	121833	CTTGGATAATTATCATAATG	70	2671
877659	N/A	N/A	124271	124290	TCTCTTGGGTTCATGCCTGA	49	2672
877683	N/A	N/A	127120	127139	TAAATATTTTTGTAGCTCTA	47	2673
877707	N/A	N/A	130019	130038	TGTTTCTAGGGACCCTGAGC	66	2674
877731	N/A	N/A	134194	134213	AAATGTTGAAATTGTTACAA	68	2675
877755	N/A	N/A	138536	138555	AAATGACAATTAGGAGGGTC	61	2676
877779	N/A	N/A	141131	141150	CTTGCAAAACTTTGTTTCAT	38	2677
877803	N/A	N/A	143288	143307	AATTTATACCAGTCTTATGT	147	2678
877827	N/A	N/A	144888	144907	ATTCTTAATTATGTGAGTCT	75	2679

표 35

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	17	222
780624	N/A	N/A	81630	81649	GCAGCATCATGCAAGCAGCA	33	674
			87887	87906			
876021	545	564	N/A	N/A	ATTTTACCTGAAGTTAGGAG	71	2680
876045	831	850	21662	21681	CATGAGGACTTCCACATTAT	56	2681
876069	1229	1248	29580	29599	TTATTTAGTGCCCAGCATGC	61	2682
876093	1474	1493	35421	35440	CTTCAGGAGAATGTATATGC	41	2683
876117	1678	1697	41911	41930	ATTCTGTATCCTCCCTGGAT	49	2684
876141	2267	2286	56275	56294	CTGTTATTCTGATCACACGC	25	2685
876165	2870	2889	71713	71732	TGTAATACGGCATCTCGGTA	24	2686
876189	3229	3248	76363	76382	GCAAGTCCAAATGTGTCAAA	30	2687
876213	3801	3820	82146	82165	GCTGATCTGATTATGGCTAA	24	2688

[0643]

876237	4149	4168	86644	86663	GGTGGTTTTACCACTCCCAG	31	2689
876261	4727	4746	92150	92169	GGCACATTTTTACGCTCCGA	10	2690
876285	5048	5067	98196	98215	TACTGTGACATGTAGTTCTT	18	2691
876309	5343	5362	100195	100214	ATAAGCTTCAGGAGACCAAT	51	2692
876333	5654	5673	101292	101311	GGAATGGTGAGCCTTGGTTG	42	2693
876357	6244	6263	124875	124894	CATTTCCTCTGGCAACTTCA	55	2694
876381	6856	6875	132566	132585	AATTGCAATACAAACAAGTG	115	2695
876405	7723	7742	145892	145911	ATAATTTTCCTATCCAAAGA	108	2696
876429	8688	8707	146857	146876	CAACTGAAAAGTGTTAGATA	67	2697
876453	N/A	N/A	4066	4085	ATACTTGGAATAGTCAAGTC	73	2698
876477	N/A	N/A	6274	6293	TAGCACAGCCATGATGAAAC	74	2699
876501	N/A	N/A	8339	8358	TTGGATCTTTTCCAGATTAA	48	2700
876525	N/A	N/A	11354	11373	AAAAGATTTAAAGTTAATGA	101	2701
876549	N/A	N/A	14435	14454	ACTTCAGTGTTTGTCACTTA	62	2702
876573	N/A	N/A	16563	16582	AATTTCTATGATTTCTGGTG	57	2703
876597	N/A	N/A	19215	19234	ACTGAGCTACTTTTGTCTTC	65	2704
876621	N/A	N/A	20798	20817	TTGGAGAATGACTTTTGCAT	77	2705
876645	N/A	N/A	23873	23892	TGCATTTCTTTATGAAAACA	26	2706
876669	N/A	N/A	26498	26517	AAAGTTACATATGACATGAC	99	2707
876693	N/A	N/A	29206	29225	AGAAGCCTTGGTCAATTATA	45	2708
876717	N/A	N/A	30957	30976	TAACTATCTCAAATTCTCAC	64	2709
876741	N/A	N/A	33365	33384	GATGTCTAACATATCATATT	39	2710
876765	N/A	N/A	34855	34874	TCACTCAGCTTTTTGGGAGT	60	2711
876789	N/A	N/A	37013	37032	TTGACTAGAATGCAGTAGGT	43	2712
876813	N/A	N/A	38806	38825	TGTATCTAGTCTCTCTCCCT	70	2713
876837	N/A	N/A	41246	41265	ATAATGTTTTCCAAACCTAA	85	2714
876861	N/A	N/A	43074	43093	CCATTAATTATTTTAAATAG	125	2715
876885	N/A	N/A	47190	47209	AAATTTCCCTCCAACAAGGT	78	2716
876909	N/A	N/A	48331	48350	ATATTAGAAGTGCAAATACT	102	2717
876933	N/A	N/A	50793	50812	CTTTAAAATCATTCCTTTAC	143	2718
876957	N/A	N/A	53340	53359	TTAGCACATTCTCTGAACTT	76	2719
876981	N/A	N/A	56553	56572	AAGATTAGACTGGATAACAC	79	2720
877005	N/A	N/A	59643	59662	ACATTTAAATAATAATGAAG	126	2721
877029	N/A	N/A	61788	61807	ATCAATGTCAGAATAGCATG	87	2722
877053	N/A	N/A	63610	63629	TGCCAAATTGTCCTCAAAAG	142	2723
877077	N/A	N/A	66573	66592	CTAGAGAAAACATTAATCTA	125	2724
877101	N/A	N/A	68563	68582	AAAATACCTTTACACAAATT	116	2725
877125	N/A	N/A	71841	71860	TTGTTCCTAGCTTTGGCATA	93	2726
877149	N/A	N/A	73151	73170	ATGGAAGGAATCATTAGGTA	47	2727
877173	N/A	N/A	74967	74986	GTATTTAGCAAGGCAAAGAA	92	2728
877197	N/A	N/A	77171	77190	AAATTGCATAAATTCATATG	114	2729
877221	N/A	N/A	79928	79947	CTGTGAAACACAATTTGGGA	60	2730
877252	N/A	N/A	84473	84492	ACATGATGTCAGTAGCTATA	41	2731
877276	N/A	N/A	87718	87737	TTCACACTAAATGGCCCCTG	81	2732
877300	N/A	N/A	90037	90056	TAATTGGATGAATAAATTTT	132	2733
877324	N/A	N/A	91380	91399	TAAGAGGATAGTTTCTACAA	57	2734
877348	N/A	N/A	93609	93628	TGGCTTGAAAACCAAGTCAT	86	2735
877372	N/A	N/A	95700	95719	TCTTTCATATCTCTTTTATC	68	2736

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877396	N/A	N/A	97476	97495	TGATCCTTGTCATGGCAGTT	36	2737
877420	N/A	N/A	100797	100816	AATCAACATTTTCTGAATCT	84	2738
877444	N/A	N/A	102597	102616	TTTATATTAAATCAATCTAA	120	2739
877468	N/A	N/A	105335	105354	AAGAGCTCTGCTACTCCATC	131	2740
877492	N/A	N/A	107501	107520	TAAAGAACTTGAGAAGGTGA	94	2741
877516	N/A	N/A	110418	110437	CCACTGTTAACTAACAGTGT	144	2742
877540	N/A	N/A	112261	112280	CTATAGCCACTACTAATCAG	109	2743
877564	N/A	N/A	114597	114616	ATTCTGAAGGCTTACTATTT	89	2744
877588	N/A	N/A	117435	117454	TTCTCTGCCCCATGATGTCA	75	2745
877612	N/A	N/A	119387	119406	GGTGATTTAATTGAGTTGCA	45	2746
877636	N/A	N/A	121878	121897	TAAATGTTCAATGTATTGTT	70	2747
877660	N/A	N/A	124436	124455	GAGAGATGAGTAGAAAGGAG	92	2748
877684	N/A	N/A	127318	127337	GCACATTATCTTTAATAAAT	84	2749
877708	N/A	N/A	130037	130056	ATAACCCATCTCAGGCTCTG	62	2750
877732	N/A	N/A	134431	134450	CTACTGTGTTCAAGATTTTA	66	2751
877756	N/A	N/A	138860	138879	AGCACAGATGGCAAAAAGCT	77	2752
877780	N/A	N/A	141161	141180	GAAATATTATATCTGTAACT	85	2753
877804	N/A	N/A	143352	143371	AATCTGCTTCTCTTGTGGGA	68	2754
877828	N/A	N/A	145005	145024	CAAATACCTTGGAACTGAAT	109	2755

표 36

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	49	222
803643	N/A	N/A	81635 87892	81654 87911	TCATTGCAGCATCATGCAAG	53	1805
876025	706	725	18605	18624	TCTCAACAAATTCAGTCAGT	55	2756
876049	836	855	21667	21686	CCACTCATGAGGACTTCCAC	55	2757
876073	1235	1254	29586	29605	AGGAGATTATTTAGTGCCCA	35	2758
876097	1478	1497	35425	35444	GCCACTTCAGGAGAATGTAT	39	2759
876121	1697	1716	41930	41949	ATATTTAGCTTATGATGAAA	93	2760
876145	2448	2467	62069	62088	ACCTTTCCCAATGCTTATCG	57	2761
876169	2890	2909	71733	71752	GCAAATTTGGTGAGCAACGC	50	2762
876193	3294	3313	76428	76447	ATCAAGATTAGCAATACAAC	105	2763
876217	3807	3826	82152	82171	CAAGATGCTGATCTGATTAT	64	2764
876241	4309	4328	87213	87232	TATAGAATTCCTCACGACCT	85	2765
876265	4732	4751	92155	92174	CAATTGGCACATTTTTACGC	79	2766
876289	5053	5072	98201	98220	TAAAATACTGTGACATGTAG	39	2767
876313	5446	5465	100435	100454	CCACAACTTGGCCCAAAAGA	68	2768
876337	5691	5710	101329	101348	GTCAGCCAAAATCAAGTCAG	48	2769
876361	6380	6399	125011	125030	GGTAATTTTCCTTGTATTTC	57	2770

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876385	6998	7017	137402	137421	GGAGTACTGACATTTCCTAT	46	2771
876409	7903	7922	146072	146091	ATAAGAAATATAACATTGTG	99	2772
876433	8823	8842	146992	147011	CCTCAAATTATTACATAGGT	60	2773
876457	N/A	N/A	4255	4274	TAAGACATCACTTTCTTTAG	58	2774
876481	N/A	N/A	6920	6939	GAATCAAATATTGGCTGTGC	115	2775
876505	N/A	N/A	8749	8768	CATATATGTACCCTCTAGAG	88	2776
876529	N/A	N/A	11687	11706	CTGATACATAGAATTACAGA	70	2777
876553	N/A	N/A	14518	14537	GCCAAAGTTTTCTCAGGGAA	54	2778
876577	N/A	N/A	16867	16886	GGGCCCACATAAATCATTCT	113	2779
876601	N/A	N/A	19369	19388	CTCTCCACTCCATGTCTCTG	75	2780
876625	N/A	N/A	21104	21123	ACAATAATGTAACATATTTT	94	2781
876649	N/A	N/A	24272	24291	AGCAAACATTTAAAAGCCCA	52	2782
876673	N/A	N/A	26747	26766	CATAATTAGATTACATAGTT	110	2783
876697	N/A	N/A	29480	29499	TTTATGAGAGTCCTACCTGC	131	2784
876721	N/A	N/A	31326	31345	TAGAAGTCCGGAAAAATATA	106	2785
876745	N/A	N/A	33421	33440	TCTTACTCAATAGTCACCTT	72	2786
876769	N/A	N/A	35273	35292	TTAGAATATTAATATAGTCC	44	2787
876793	N/A	N/A	37536	37555	ACTGATCTGATTCAATGGTA	96	2788
876817	N/A	N/A	38963	38982	CAGAACAAAGTATCATCCCT	88	2789
876841	N/A	N/A	41339	41358	CTTTATTAAGCTACACTGTA	82	2790
876865	N/A	N/A	43282	43301	AGATAAATTTAACCCATTAC	95	2791
876889	N/A	N/A	47322	47341	ACGAATCATGCCACAGTGAA	95	2792
876913	N/A	N/A	48676	48695	TACTAGAACACAGTGAAATG	119	2793
876937	N/A	N/A	51449	51468	AATACATAGTCTCCCTTGAC	95	2794
876961	N/A	N/A	53597	53616	ATTCTTAATCTCCCGTGAAC	74	2795
876985	N/A	N/A	56874	56893	CATGGTTCAGGAGGGAAGAG	107	2796
877009	N/A	N/A	59869	59888	TCCTTGGAGGATCCAAACTA	99	2797
877033	N/A	N/A	62406	62425	TCATAAAGAACTTAAATGTC	135	2798
877057	N/A	N/A	64411	64430	ATGGGAAATTATCCCGAAGC	133	2799
877081	N/A	N/A	66847	66866	CAAAATACTTCAACACTTCA	119	2800
877105	N/A	N/A	68855	68874	AATATAACAAAAATCTGATT	126	2801
877129	N/A	N/A	72099	72118	AACCCACACCATTAGGTAGA	90	2802
877153	N/A	N/A	73877	73896	TGCAAAAACCAGAGGCACGG	78	2803
877177	N/A	N/A	75128	75147	TTTTAAATCAAATTGGATGA	143	2804
877201	N/A	N/A	77744	77763	CCCCTCTATAGTATACAAAA	94	2805
877225	N/A	N/A	80668	80687	TTAACCTGGAAGCTAAACAG	149	2806
877256	N/A	N/A	84735	84754	TGAGAGGTGATGACAGAGCT	99	2807
877280	N/A	N/A	87905	87924	TGCACAGAAGAGTTCATTGC	86	2808
877304	N/A	N/A	90343	90362	TAAAAAGTTGTCTTCAAAGG	87	2809
877328	N/A	N/A	91620	91639	CTTGGTTATTTGTAAAATGT	37	2810
877352	N/A	N/A	93973	93992	TTATGTCAAAGCTACAGAGA	60	2811
877376	N/A	N/A	95796	95815	TTTTCCAAATTCCTTTGTAT	58	2812
877400	N/A	N/A	97827	97846	GAAACAATGAACATCAGTAT	80	2813
877424	N/A	N/A	101020	101039	AACTGCTGCAGACTACCAGA	82	2814
877448	N/A	N/A	102830	102849	AGCATTTAAATTCAACCTAA	133	2815
877472	N/A	N/A	105422	105441	GTAAGGTTGAGAACAAGTGC	80	2816
877496	N/A	N/A	108081	108100	AGTAGATTCTGTTATACAAA	53	2817
877520	N/A	N/A	110838	110857	AAAAGAGATTATGTCAGATT	86	2818

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877544	N/A	N/A	112426	112445	GTACTGTCAGAATTAAATTT	76	2819
877568	N/A	N/A	115091	115110	GATTTGTTATTTAAAGTAAG	166	2820
877592	N/A	N/A	117565	117584	ACAGTGTAAAGTTTTCATCT	58	2821
877616	N/A	N/A	119914	119933	GAGTTGCATATGGTTTAGGA	36	2822
877640	N/A	N/A	122283	122302	TTCTCATCCAGTGCACACAT	81	2823
877664	N/A	N/A	124843	124862	CCTGAAAGTAAGCAGATAAA	141	2824
877688	N/A	N/A	127923	127942	AATTCATGCCATTCCAGAAT	143	2825
877712	N/A	N/A	132134	132153	ATAAGAAGATTGTTCCTCTC	84	2826
877736	N/A	N/A	135027	135046	AGAGAAATAAATGCTCATGG	82	2827
877760	N/A	N/A	139725	139744	TATGGAACTTTAAAGAGTTA	93	2828
877784	N/A	N/A	141305	141324	ACTTTACTTACTTTTGGTTA	81	2829
877808	N/A	N/A	143492	143511	AGACTATGATTAAAACAAAC	88	2830
877832	N/A	N/A	145211	145230	ACATCATTGCCCTGTTTGGA	55	2831

표 37

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	34	222
876026	711	730	18610	18629	TTTGTTCTCAACAAATTCAG	45	2832
876050	837	856	21668	21687	GCCACTCATGAGGACTTCCA	25	2833
876074	1236	1255	29587	29606	AAGGAGATTATTTAGTGCCC	41	2834
876098	1480	1499	35427	35446	CAGCCACTTCAGGAGAATGT	33	2835
876122	1698	1717	41931	41950	CATATTTAGCTTATGATGAA	66	2836
876146	2449	2468	62070	62089	CACCTTTCCCAATGCTTATC	44	2837
876170	2931	2950	72955	72974	TTCATGATCAAAAATGGGCC	44	2838
876194	3333	3352	76467	76486	ATCTAAAACCACTGAGGGTC	59	2839
876218	3835	3854	82180	82199	ACCATAAATATGCTTTTTCA	36	2840
876242	4311	4330	87215	87234	ACTATAGAATTCCTCACGAC	45	2841
876266	4733	4752	92156	92175	TCAATTGGCACATTTTTACG	71	2842
876290	5067	5086	98215	98234	TTTTTCTAGGAGCTTAAAAT	90	2843
876314	5447	5466	100436	100455	TCCACAACTTGGCCCAAAAG	75	2844
876338	5692	5711	101330	101349	GGTCAGCCAAAATCAAGTCA	76	2845
876362	6427	6446	126543	126562	TCTCAACCATAGGCCATGGG	36	89
876386	7041	7060	137445	137464	ATTTCTTTCCGTTGAATTTG	71	2846
876410	7993	8012	146162	146181	ATCGGCCTTATAAATTTTAG	56	2847
876434	8862	8881	147031	147050	AAGAATTTACCGAAAGTACT	88	2848
876458	N/A	N/A	4345	4364	AAATTTCTGGGTTTCCTATG	78	2849
876482	N/A	N/A	7014	7033	AGCTCTTTGATCCTCAGTGA	43	2850
876506	N/A	N/A	8763	8782	AAAAAGAGAAAGTGCATATA	97	2851
876530	N/A	N/A	11858	11877	TGTACAGGAATATGACTAGA	73	2852

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[0648]

876554	N/A	N/A	14745	14764	TCCAGCCTCTCTCATGCTAT	94	2853
876578	N/A	N/A	16881	16900	TGATAACTGACACAGGGCCC	91	2854
876602	N/A	N/A	19380	19399	GGCCCTTCATGCTCTCCACT	81	2855
876626	N/A	N/A	21285	21304	AGATAAATAAATTGGAGGGT	76	2856
876650	N/A	N/A	24302	24321	ATATTTTTAAGCCCACATTG	83	2857
876674	N/A	N/A	27099	27118	TCATCAACGGCCTCACAATC	114	2858
876698	N/A	N/A	29500	29519	AATTTTGAATAACTCTAATA	115	2859
876722	N/A	N/A	31348	31367	ATGTCATGTGTGAGTTTACA	46	2860
876746	N/A	N/A	33423	33442	GGTCTTACTCAATAGTCACC	55	2861
876770	N/A	N/A	35317	35336	ACTTATAGATATGAAAGCAT	86	2862
876794	N/A	N/A	37818	37837	AAAGATTTACATTTAGTCGA	67	2863
876818	N/A	N/A	39048	39067	ATATAACTAGAGAAAATGAT	118	2864
876842	N/A	N/A	41389	41408	AAGTTCTGTAAAGGCTATAT	65	2865
876866	N/A	N/A	43424	43443	AAAGAAAAGAACCAAGGTTT	67	2866
876890	N/A	N/A	47351	47370	GCATTTAGTTTGTTGCCACA	30	2867
876914	N/A	N/A	48782	48801	CTAATAAAGTGGATGGATTT	117	2868
876938	N/A	N/A	51461	51480	TATCATCTTAATAATACATA	66	2869
876962	N/A	N/A	53654	53673	CTCTTGAAGAAAAACTATTT	96	2870
876986	N/A	N/A	56900	56919	AGAACAATCAGATAGATATA	105	2871
877010	N/A	N/A	59885	59904	TTTGTGGAAGGAATTTTCCT	73	2872
877034	N/A	N/A	62466	62485	GTACCCCTTCAAAAAGCTTC	97	2873
877058	N/A	N/A	64464	64483	CACTATACCCATATACCCAA	84	2874
877082	N/A	N/A	67017	67036	GAAAACTGCATTTCACCAAG	67	2875
877106	N/A	N/A	69629	69648	TTATCCAGAAAATCTCCAAA	99	2876
877130	N/A	N/A	72373	72392	TCCATAGTTCCAAAACAGAC	76	2877
877154	N/A	N/A	73916	73935	CAAAGATGCTCCTGAACATC	87	2878
877178	N/A	N/A	75204	75223	CACTGGGAATAGACAGAAAC	68	2879
877202	N/A	N/A	77774	77793	GGTTTTGACAAGTGTACCAT	57	2880
877226	N/A	N/A	80802	80821	ACCAATAGTGTGTCACTTAA	48	2881
877233	N/A	N/A	81930	81949	ACTAGCATTATTGACATATG	98	2882
877257	N/A	N/A	84787	84806	TAGTGAGTGAACACAGCCAT	48	2883
877281	N/A	N/A	87933	87952	TCCTGACACAAGCTTTTTAA	64	2884
877305	N/A	N/A	90378	90397	CTGGTATTTCTCAAAGCATT	40	2885
877329	N/A	N/A	91655	91674	TTTTAAATATTCAAGGTAAA	96	2886
877353	N/A	N/A	94061	94080	AATGTGCAACAAAGAATTAT	74	2887
877377	N/A	N/A	95892	95911	CATTATCTTGACTTTATCAC	78	2888
877401	N/A	N/A	98295	98314	TAGCAATTAATTTTTTAAGG	95	2889
877425	N/A	N/A	101246	101265	AGAAGTAATAAAACATTTTT	140	2890
877449	N/A	N/A	103447	103466	GGGAGAGTAATCACAAACAT	76	2891
877473	N/A	N/A	105724	105743	TCTCCTGTTCAGAAACAAAT	103	2892
877497	N/A	N/A	108130	108149	GTTTAGAGCAGTAAGTCATG	65	2893
877521	N/A	N/A	110906	110925	TAAAATTTGAAATGCATGCT	118	2894
877545	N/A	N/A	112696	112715	TACTTAACGAAGATTAAATA	106	2895
877569	N/A	N/A	115659	115678	CAAATGCATACTTGCTTTCG	71	2896
877593	N/A	N/A	117566	117585	AACAGTGTAAAGTTTTCATC	65	2897
877617	N/A	N/A	119915	119934	AGAGTTGCATATGGTTTAGG	39	2898
877641	N/A	N/A	122290	122309	TTCTAAATTCTCATCCAGTG	61	2899
877665	N/A	N/A	125117	125136	ATGATCATCTGTTTAAGGAA	74	2900

877689	N/A	N/A	128242	128261	AGCATAAACAAGAAGGAGAA	80	2901
877713	N/A	N/A	132213	132232	AGTTTTGCCTATCAAGATGA	82	2902
877737	N/A	N/A	135443	135462	CCTAAGCACCCATGAATGAA	79	2903
877761	N/A	N/A	139807	139826	AATCTCTTTTGGGAGATGAG	81	2904
877785	N/A	N/A	141341	141360	TAACCATTCTGAATTGAATA	86	2905
877809	N/A	N/A	143723	143742	AATTATTATCAAAGGAAGAC	126	2906
877833	N/A	N/A	145245	145264	AATTTATGAAACACATAATA	101	2907

표 38

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	15	222
803630	N/A	N/A	81592	81611	AAAGCCATAGTGTTTGAAGG	66	1792
			87849	87868			
876015	341	360	3732	3751	ACCTGCTGCACACTCGCGAC	39	2908
876039	824	843	N/A	N/A	ACTTCCACATTATTGCAAGG	38	2909
876063	1038	1057	28013	28032	CGCTGAGATCTGCAATGCTG	66	2910
876087	1467	1486	35414	35433	AGAATGTATATGCTTCTGCA	75	2911
876111	1499	1518	35446	35465	AGCATTTTACAGCCACTTTC	50	2912
876135	2086	2105	56020	56039	AAGATGCTGACAATTTGAGG	66	2913
876159	2716	2735	65554	65573	ATTTAGACAGCACATCTTCA	76	2914
876183	3222	3241	76356	76375	CAAATGTGTCAAACTCTTCA	42	2915
876207	3752	3771	82097	82116	CAGTGTGCGGGACCTGGTAG	52	2916
876231	3973	3992	83968	83987	ATTTCCCCATTTCATTGGGA	74	2917
876255	4604	4623	88705	88724	CGAAGTTTTGCCAAAGCATC	37	2918
876279	4962	4981	98110	98129	TTTTGGACAACCTTCCACTT	51	2919
876303	5197	5216	99203	99222	AAGGCATTTCATATAGTCGG	31	2920
876327	5646	5665	101284	101303	GAGCCTTGGTTGATCTGGAT	41	2921
876351	6067	6086	N/A	N/A	TGGCTGAGTGGAGGTATCTC	100	2922
876375	6733	6752	132443	132462	TTTCAACAGGAAGATGCACC	68	2923
876399	7490	7509	143138	143157	AGCTGTGCTGTCATCATGAC	77	2924
876423	8494	8513	146663	146682	AAAAATATCACTTGAAGGAC	76	2925
876447	N/A	N/A	3735	3754	TTTACCTGCTGCACACTCGC	44	2926
876471	N/A	N/A	5332	5351	TATACATGTATCAAATAGCA	56	2927
876495	N/A	N/A	7824	7843	ATCTCTCTAAGAGAGAAGGT	110	2928
876519	N/A	N/A	10780	10799	TCTCTTCATGGTTTGAATTC	72	2929
876543	N/A	N/A	13667	13686	AAGTTTGCTTATTTGCATTT	75	2930
876567	N/A	N/A	15828	15847	TAATTTCATGAGTCTCAATC	89	2931
876591	N/A	N/A	17978	17997	CATGTATAAAATTATAGTTT	72	2932
876615	N/A	N/A	20147	20166	CAATGTGGGTGGAAAACAAT	107	2933

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[0650]

876639	N/A	N/A	23039	23058	ATAGACAATGACCCTTGCTC	38	2934
876663	N/A	N/A	26161	26180	TTCTCATGAAAAATAATGAA	80	2935
876687	N/A	N/A	28159	28178	TGAGCTACACAGGACAGAAA	90	2936
876711	N/A	N/A	30793	30812	CAAAAGCATATGCAGCAGAG	47	2937
876735	N/A	N/A	32754	32773	ATCAAAGGAGATTTCCAGGT	33	2938
876759	N/A	N/A	34066	34085	AATAAGTAGTCTATCTTAAG	101	2939
876783	N/A	N/A	36564	36583	TCCGCTGTGTTTTTGCCTCA	65	2940
876807	N/A	N/A	38580	38599	ATGCCTCACTCACCCCCGAC	70	2941
876831	N/A	N/A	40880	40899	AAGAAGATGTGACCACTAAA	122	2942
876855	N/A	N/A	42917	42936	GTAATTCCCTTCTTCTCTTT	47	2943
876879	N/A	N/A	46712	46731	AATACTATTGTTATTTTTAC	126	2944
876903	N/A	N/A	48099	48118	CAGGGTGCATAGTCTGTAGG	49	2945
876927	N/A	N/A	50346	50365	TCTGAACTTTCTGTTTGATT	35	2946
876951	N/A	N/A	52863	52882	GCCCTACAAAAATCTATTCT	53	2947
876975	N/A	N/A	56130	56149	GGATGCAAGTGAAAAACACT	103	2948
876999	N/A	N/A	57946	57965	CTAGATATAAATAACCTCTG	52	2949
877023	N/A	N/A	61194	61213	ATAATATCCATCAGTTACTG	97	2950
877047	N/A	N/A	63254	63273	GAAGAGACAGCCAGGTGAAG	126	2951
877071	N/A	N/A	66298	66317	ACAATATTTTGGAACAACTC	51	2952
877095	N/A	N/A	67597	67616	ATAGGTAATATGATTTAATT	127	2953
877119	N/A	N/A	71046	71065	TCATGTTTCATGGTTTCTTT	31	2954
877143	N/A	N/A	72871	72890	GGAAGGAACCATGAAATTTT	74	2955
877167	N/A	N/A	74441	74460	CCTTGAGAATTTAACAATTT	44	2956
877191	N/A	N/A	76594	76613	CTCTTTCTTACCCTTCTAAA	143	2957
877215	N/A	N/A	79222	79241	GCAAAGCAAACAGATTTTGA	49	2958
877246	N/A	N/A	83653	83672	TCACTCATCTGTAATATTAA	34	2959
877270	N/A	N/A	86973	86992	CTAACATATCCCTCCATGTT	69	2960
877294	N/A	N/A	89174	89193	CCATAAAACAGGAATTCCAA	84	2961
877318	N/A	N/A	91036	91055	ATCTCTTAACCCAGAGAATT	93	2962
877342	N/A	N/A	93085	93104	ATATTTGAGACACTGACATG	107	2963
877366	N/A	N/A	95216	95235	AATTACTCCACAGAATCTTC	104	2964
877390	N/A	N/A	96680	96699	AATTCTAACTCTACCTCTTC	140	2965
877414	N/A	N/A	99835	99854	TAAAAAGAAGTTTTTGATCA	100	2966
877438	N/A	N/A	102077	102096	ATGTGCAGGAAGTCAAGATA	63	2967
877462	N/A	N/A	104952	104971	GTATTATTTGCATCTTATCA	57	2968
877486	N/A	N/A	106807	106826	AGTGAGTCTTACAAAAAGTT	73	2969
877510	N/A	N/A	110180	110199	GAGAAAAGCACAGATGACTC	46	2970
877534	N/A	N/A	111786	111805	CTCTGCAATTCAAAAAAAGT	100	2971
877558	N/A	N/A	114104	114123	TAGGCAATGAGAGATGATAC	147	2972
877582	N/A	N/A	117147	117166	CAGCTGAAGATTCTCTCTCT	66	2973
877606	N/A	N/A	119182	119201	TCAGGATTGGGAACTAAGAA	56	2974
877630	N/A	N/A	121116	121135	TTCTCTAAACTTTAGTCTCT	53	2975
877654	N/A	N/A	123425	123444	TACTCTTTCAACTGTTCTTT	61	2976
877678	N/A	N/A	126753	126772	GGATGGTGAAAATTATAGGA	61	2977
877702	N/A	N/A	129321	129340	TTCTATATTGCAGAGCCACC	131	2978
877726	N/A	N/A	133413	133432	TTCAGTGGAGTTTAGTTCAG	81	2979
877750	N/A	N/A	138222	138241	CCAAGTTCACAAAACCAATA	57	2980
877774	N/A	N/A	140803	140822	ATGGCAAACTCCTACTTGGC	97	2981

877798	N/A	N/A	142508	142527	TTTTCCCAGAACCAGTGAAT	102	2982
877822	N/A	N/A	144769	144788	TTTGGATATGGTAAGGTACA	71	2983

표 39

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	18	222
803628	N/A	N/A	81589	81608	GCCATAGTGTTTGAAGGAAT	43	1790
			87846	87865			
876012	338	357	3729	3748	TGCTGCACACTCGCGACTCT	71	2984
876036	802	821	18701	18720	TCGCTAGGGAATGTAAACAA	63	2985
876060	877	896	21708	21727	CTTTCATAGCTTCCACCACA	56	2986
876084	1450	1469	35397	35416	GCATTAACTCCAAAACATTC	32	2987
876108	1491	1510	35438	35457	ACAGCCACTTTCAGCCACTT	63	2988
876132	1957	1976	52997	53016	CATTCTTCTTTGTAATCAAG	53	2989
876156	2621	2640	N/A	N/A	GCTAGTGTAGATGCTATATT	26	2990
876180	3215	3234	N/A	N/A	GTCAAACTCTTCAGAGTTTC	21	2991
876204	3660	3679	80940	80959	GGAAAATTTGTTCTGAGATA	20	2992
876228	3924	3943	83919	83938	ATCCAGAGATGTCAGATTTT	131	2993
876252	4427	4446	N/A	N/A	GCGCGAGCCTTTATATTGAA	95	2994
876276	4816	4835	92239	92258	CGTGAGGAAGCTCATTTTCA	30	148
876300	5193	5212	99199	99218	CATTTCATATAGTCGGATGA	46	2995
876324	5571	5590	100560	100579	TTGATGTTCTTCACCATCAT	57	2996
876348	5984	6003	113181	113200	TGCTGAAGCAGGCGATCCAA	97	2997
876372	6650	6669	129795	129814	TCAAGAAATGAGAGCTGTCC	87	2998
876396	7395	7414	143043	143062	TCCTCCAGTTCCTATCCAAA	87	2999
876420	8397	8416	146566	146585	ATGTCTAGGAAAGACACAGA	119	3000
876444	9175	9194	147344	147363	ATTTAAATATGGTATTCATT	145	3001
876468	N/A	N/A	5184	5203	ACTCATAACTACTCCGGACA	101	3002
876492	N/A	N/A	7482	7501	TGGCAGTCTGGAATATCATG	62	3003
876516	N/A	N/A	10656	10675	AATCAAACTTCTGAGTTTAA	78	3004
876540	N/A	N/A	13053	13072	AGCACTACTTATTTTCCAAT	34	3005
876564	N/A	N/A	15510	15529	AGGCACCTTCATTCCTATTG	63	3006
876588	N/A	N/A	17889	17908	TTTTAATTTTATGCCAGAGT	42	3007
876612	N/A	N/A	19937	19956	TTGTGATTTTATAAACATCA	72	3008
876636	N/A	N/A	22628	22647	TTAACCCTTATTTATATATG	104	3009
876660	N/A	N/A	25657	25676	TTATATACATCTGTGTATAA	85	3010
			25687	25706			
			25717	25736			
			25747	25766			

[0651]

			25811 25875	25830 25894			
876684	N/A	N/A	27860	27879	TTAACATATAACACTATTTA	119	3011
876708	N/A	N/A	30296	30315	CAGAGGATACCCATTGCAAA	60	3012
876732	N/A	N/A	32607	32626	CCTCTTTAACTGCACAGTAG	38	3013
876756	N/A	N/A	33886	33905	AACCTTTCCCAAAGTGGCTA	56	3014
876780	N/A	N/A	36392	36411	TAACCCTACTTCTTACAAGT	109	3015
876804	N/A	N/A	38436	38455	CATCGATATTCTCAAAGCCT	45	3016
876828	N/A	N/A	40375	40394	TACTTAAAATACTTCAAACA	110	3017
876852	N/A	N/A	42387	42406	ACCATATACTATGAGACCAG	40	3018
876876	N/A	N/A	45845	45864	GGAATTACAGTGGAGAGGTT	107	3019
876900	N/A	N/A	48095	48114	GTGCATAGTCTGTAGGTAGT	28	3020
876924	N/A	N/A	50233	50252	GCTCTGTTGTCACCCTTGTA	62	3021
876948	N/A	N/A	52394	52413	CATTAGAAGATGAATTCACT	104	3022
876972	N/A	N/A	55581	55600	ATAATATTGAACAGTAGGTT	84	3023
876996	N/A	N/A	57799	57818	CTGTTGGGTAGAAAGATTTG	85	3024
877020	N/A	N/A	60838	60857	GGTTGGAAGGCACCAATTAA	76	3025
877044	N/A	N/A	63123	63142	AGCCTACTGAGCGGTTGGAA	82	3026
877068	N/A	N/A	66018	66037	GTTGCAGACATTTTACATAC	32	3027
877092	N/A	N/A	67322	67341	TAGAACCATACCTAAATAGT	97	3028
877116	N/A	N/A	70348	70367	GTAATACCCGAAAGAAGGGA	53	3029
877140	N/A	N/A	72680	72699	TGAAAAAGCTATATCCATAT	120	3030
877164	N/A	N/A	74213	74232	AAAAAAAACTTTCAGTAATC	142	3031
877188	N/A	N/A	76212	76231	AACACAATCCACAACAGAAT	89	3032
877212	N/A	N/A	78681	78700	AGGAGGAAAATACTATCCAA	59	3033
877243	N/A	N/A	83326	83345	TATATGCACAGTTTTGCTGA	71	3034
877267	N/A	N/A	86866	86885	AGAACAGAAAGCTCAGTTTT	80	3035
877291	N/A	N/A	89005	89024	CTCTCAGAAACATTTTCTCA	66	3036
877315	N/A	N/A	90693	90712	AACAAAACTTAAAAGTGTCT	166	3037
877339	N/A	N/A	92828	92847	AAACAACTCACACATTTCTA	84	3038
877363	N/A	N/A	95003	95022	AGTTGAGTTACCTCCTGATA	72	3039
877387	N/A	N/A	96290	96309	TCTGGTTACTAGAATGTAGC	104	3040
877411	N/A	N/A	99458	99477	GATTGCCTACTCCAAGGTTT	56	3041
877435	N/A	N/A	101844	101863	AGGCTTTTAATGAATATTTC	80	3042
877459	N/A	N/A	104859	104878	GGTATTGAGAGAGCTTCAGA	51	3043
877483	N/A	N/A	106692	106711	GAAAAGACAAACTAGGATTG	70	3044
877507	N/A	N/A	109824	109843	GTAGAACAGAGTCTGAAGTA	67	3045
877531	N/A	N/A	111551	111570	CTGTAACTCTGTTGAAATGT	96	3046
877555	N/A	N/A	113739	113758	TCAAAGACCACAGCCTTTCC	116	3047
877579	N/A	N/A	116515	116534	GCTAAGAGACTTCTTTCTTC	48	3048
877603	N/A	N/A	118863	118882	ACTAAAGTTTTTGCTGTTAC	51	3049
877627	N/A	N/A	120815	120834	CGGAAAAGACAAGAAGATAA	82	3050
877651	N/A	N/A	122955	122974	TTATCATGTGAATTAGCATA	47	3051
877675	N/A	N/A	126419	126438	CCAGACATTGCAAAGAAAAA	65	3052
877699	N/A	N/A	129171	129190	AGTGTGAAGGCACCGTAAGA	73	3053
877723	N/A	N/A	133344	133363	CCAATTCCATCCATTGAAAT	69	3054
877747	N/A	N/A	137747	137766	AAAAGTGATTAGGTTGAGTG	62	3055
877771	N/A	N/A	140595	140614	TATTTTCTACATACCCCTCG	93	3056

[0652]

877795	N/A	N/A	142281	142300	ATCTAAAATGTTCTCAAGAG	136	3057
877819	N/A	N/A	144428	144447	GTTGGCTTCTCAGAGGTTTT	50	3058

표 40

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	24	222
803632	N/A	N/A	81595	81614	TAAAAAGCCATAGTGTTTGA	91	1794
			87852	87871			
876018	441	460	10465	10484	ACCAAGGACTTCCCAATCAT	69	32
876042	828	847	21659	21678	GAGGACTTCCACATTATTGC	19	3059
876066	1105	1124	29366	29385	TCTCATTCTTTTCCTCTAAA	30	3060
876090	1471	1490	35418	35437	CAGGAGAATGTATATGCTTC	25	3061
876114	1580	1599	37629	37648	CGTTTCATAACTGTTAGTAT	46	3062
876138	2218	2237	56226	56245	CATCCATAGCTACTTTTGCA	54	3063
876162	2848	2867	71691	71710	ATTCTCCTACACTAATTGAA	64	3064
876186	3225	3244	76359	76378	GTCCAAATGTGTCAAACTCT	20	3065
876210	3797	3816	82142	82161	ATCTGATTATGGCTAAATAA	48	3066
876234	4048	4067	84043	84062	TGGCTTTACATCCTATATGT	43	3067
876258	4692	4711	92115	92134	AAGTTCTACATAGCAGTCTG	34	3068
876282	5044	5063	98192	98211	GTGACATGTAGTTCTTTGGA	11	3069
876306	5201	5220	99207	99226	AAATAAGGCATTTCATATAG	56	3070
876330	5650	5669	101288	101307	TGGTGAGCCTTGGTTGATCT	42	3071
876354	6155	6174	118488	118507	TAGTCAGCAATCTTTGCAAT	96	3072
876378	6782	6801	132492	132511	ATGACCAGGAGAGTACCAGA	69	3073
876402	7537	7556	145140	145159	TTTTCCGGTTGTAGCCCAAT	70	3074
876426	8594	8613	146763	146782	TGTAGGATCTGCAGCATCAC	60	3075
876450	N/A	N/A	3743	3762	ACAATGCCTTTACCTGCTGC	98	3076
876474	N/A	N/A	5889	5908	TACTTCAGCCCAGGATTGCA	70	3077
876498	N/A	N/A	7911	7930	CTACATGGAACTTCTGTGAT	71	3078
876522	N/A	N/A	10992	11011	CAGATGTGCTGAAAGTTAAT	62	3079
876546	N/A	N/A	14076	14095	ATGAGATTTTTGAGAGGCAA	107	3080
876570	N/A	N/A	15984	16003	AATTTTTACATGAAGACTGT	83	3081
876594	N/A	N/A	18271	18290	CTAGAGAAAACTGACAGTGA	80	3082
876618	N/A	N/A	20538	20557	AAAGACTCTACCAGAAAAAG	106	3083
876642	N/A	N/A	23590	23609	AATGTATGGTGACTTGACCT	97	3084
876666	N/A	N/A	26378	26397	AACAAAACCACTTCTTCTTC	69	3085
876690	N/A	N/A	28864	28883	TGAAGAGAAAACCACACACT	50	3086
876714	N/A	N/A	30858	30877	TTATAGTTCATTTTTTAAGA	159	3087
876738	N/A	N/A	32945	32964	ACTCCAAAGACAATACAAAA	102	3088
876762	N/A	N/A	34263	34282	CAACTGGCCAATTTTCCTCT	60	3089

[0653]

876786	N/A	N/A	36893	36912	GATACATTCCTTCTTTTCCA	50	3090
876810	N/A	N/A	38645	38664	CCTTTTCTTTGGGCCTCAGC	55	3091
876834	N/A	N/A	40906	40925	ACTTCTGAGGCTGCCTATTA	102	3092
876858	N/A	N/A	42989	43008	CCAATTCATCTTATGCAAAA	50	3093
876882	N/A	N/A	46918	46937	ATTTCCTGAGCCACCCTTCT	62	3094
876906	N/A	N/A	48113	48132	ATTAAGTACTTGTCCAGGGT	41	3095
876930	N/A	N/A	50500	50519	GACACAGAGAGCTGTGAGCA	73	3096
876954	N/A	N/A	53300	53319	GAATAACCATGCTGACTTTA	66	3097
876978	N/A	N/A	56491	56510	AAGACACAAACAATTGCAAT	98	3098
877002	N/A	N/A	59243	59262	TGATAGAAGTGTTTGGTTTT	60	3099
877026	N/A	N/A	61360	61379	GGTTAGCATGTGAGGTGCCA	83	3100
877050	N/A	N/A	63441	63460	AAGGTTACAACCATGAACAA	158	3101
877074	N/A	N/A	66455	66474	ATATTGCATAACTTAATAGC	106	3102
877098	N/A	N/A	68250	68269	AGAGCATTTTTCAACACCTA	13	3103
877122	N/A	N/A	71326	71345	ATAGTCCAGCAGGAAAAAGC	81	3104
877146	N/A	N/A	73085	73104	TGAATAATTGGAGGAAATTC	98	3105
877170	N/A	N/A	74875	74894	CTCTGTCTCCAGATATAAAA	27	3106
877194	N/A	N/A	77081	77100	AATTAGTTGTAAAAATGTAA	118	3107
877218	N/A	N/A	79715	79734	CAGGACACTCCTAGAAGCTG	44	3108
877249	N/A	N/A	84418	84437	TGCTATATGAAATACAGTGT	58	3109
877273	N/A	N/A	87070	87089	GACCATGTTTAGAGAACTAT	48	3110
877297	N/A	N/A	89927	89946	TTACATGACATTACCATCTA	50	3111
877321	N/A	N/A	91204	91223	CAGAATTTCTGCTTAAATTC	56	3112
877345	N/A	N/A	93276	93295	GAAACATGGAATCTAGAACA	150	3113
877369	N/A	N/A	95294	95313	CAAATTAACTTAATTTTTAC	125	3114
877393	N/A	N/A	97092	97111	GCCCAAGGACTTGTCTTACC	52	3115
877417	N/A	N/A	100614	100633	GTATCAAAACATACCTTCCT	108	3116
877441	N/A	N/A	102459	102478	TTCTCACCACATAAATATTT	67	3117
877465	N/A	N/A	105189	105208	CCTTGAAATGTAGTCACTTG	61	3118
877489	N/A	N/A	107021	107040	ACAGAAGGCGAAGTCAGGAG	90	3119
877513	N/A	N/A	110256	110275	GGCCACAGTGATCAGTTTGG	56	3120
877537	N/A	N/A	112156	112175	AAAAAATACATATCATCCCC	124	3121
877561	N/A	N/A	114361	114380	ATAATCCTTTATAATAAGTA	118	3122
877585	N/A	N/A	117351	117370	CACAAGACTTAATGGAGTTA	61	3123
877609	N/A	N/A	119274	119293	AACAAATGCCAACCCCTAAA	103	3124
877633	N/A	N/A	121503	121522	TATAGTATTTATATGGGTGT	50	3125
877657	N/A	N/A	124119	124138	ACAAAGGGAAATGGTTAAAC	40	3126
877681	N/A	N/A	126991	127010	ACGGGCACCCTACAAGAAAT	117	3127
877705	N/A	N/A	129885	129904	AGTAACTTTCCAAATGGTAT	69	3128
877729	N/A	N/A	134033	134052	CTCTGCCCCTTTTCCCAGAC	83	3129
877753	N/A	N/A	138357	138376	TTACCAGGTGCTGGTCATTA	24	3130
877777	N/A	N/A	140907	140926	ATAAAGAAAAATTACGAACA	79	3131
877801	N/A	N/A	142946	142965	TTTACCATTACCTCCCTAGA	61	3132
877825	N/A	N/A	144861	144880	CAGCTTAACCTTTCTATAAA	60	3133

[0654]

표 41

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

[0655]

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	16	222
876020	528	547	13794	13813	GAGGAGATCTAAGGTCTTCA	35	2603
876044	830	849	21661	21680	ATGAGGACTTCCACATTATT	47	2604
876068	1161	1180	29422	29441	ACAGGCTTCCAGCCAAAACA	63	2605
876092	1473	1492	35420	35439	TTCAGGAGAATGTATATGCT	46	2606
876116	1637	1656	37686	37705	ATAAAATGTAAAATAGCTCG	112	2607
876140	2262	2281	56270	56289	ATTCTGATCACACGCTCTCT	42	2608
876164	2869	2888	71712	71731	GTAATACGGCATCTCGGTAA	66	2609
876188	3228	3247	76362	76381	CAAGTCCAAATGTGTCAAAC	58	2610
876212	3800	3819	82145	82164	CTGATCTGATTATGGCTAAA	59	2611
876236	4144	4163	86639	86658	TTTTACCACTCCCAGTATTT	114	2612
876260	4725	4744	92148	92167	CACATTTTTACGCTCCGATA	31	2613
876284	5046	5065	98194	98213	CTGTGACATGTAGTTCTTTG	39	2614
876308	5338	5357	100190	100209	CTTCAGGAGACCAATTTAAG	48	2615
876332	5652	5671	101290	101309	AATGGTGAGCCTTGGTTGAT	57	2616
876356	6204	6223	118537	118556	GCCCTCTGATGTTTTTATCC	98	2617
876380	6826	6845	132536	132555	TCATCTTTTCTAGGGTATGT	43	2618
876404	7660	7679	145829	145848	TTTCAGCTAATTCTTTTCTC	56	2619
876428	8683	8702	146852	146871	GAAAAGTGTTAGATATTTAT	135	2620
876452	N/A	N/A	3761	3780	GAATGAGTTGAAGTGAAAAC	120	2621
876476	N/A	N/A	6208	6227	ATCCAGTAATCTCATCGCTG	47	2622
876500	N/A	N/A	8095	8114	ATTCTGAACAGCTTCTGGTG	136	2623
876524	N/A	N/A	11128	11147	TTTTCCTGGAAACACATTCT	114	2624
876548	N/A	N/A	14203	14222	AAGGGCAGGAATGACCACTA	72	2625
876572	N/A	N/A	16432	16451	GCAATTGAAGAAAGTCTACT	56	2626
876596	N/A	N/A	18903	18922	GTTTCTCCAGCACCAAGCCC	49	2627
876620	N/A	N/A	20690	20709	TTCCAGAAGGGCAACCAATG	100	2628
876644	N/A	N/A	23667	23686	GAACTGGACAAGTTAATCCT	47	2629
876668	N/A	N/A	26426	26445	TGCTGTTCTAGACAATTTGG	46	2630
876692	N/A	N/A	29204	29223	AAGCCTTGGTCAATTATAAA	91	2631
876716	N/A	N/A	30940	30959	CACTTGCCATTATCAAATAT	84	2632
876740	N/A	N/A	33139	33158	TGTATGCAACCTTGGGACCT	57	2633
876764	N/A	N/A	34714	34733	TGGAAAGCATTTACATAGAA	47	2634
876788	N/A	N/A	36957	36976	TGTTAACTGAAACTTGTGCA	70	2635
876812	N/A	N/A	38785	38804	TCTATCATCCTCTGCACCAC	69	2636
876836	N/A	N/A	41061	41080	TAAGGAAGGCAGCCTTGATA	54	2637
876860	N/A	N/A	43045	43064	TTTATAAAAATGTTCACACT	112	2638
876884	N/A	N/A	47090	47109	AATCTCATCCATCTGTAATT	50	2639
876908	N/A	N/A	48315	48334	TACTCTGATTTCCTCATCTT	58	2640

876932	N/A	N/A	50766	50785	CTTTACAATGTCTTCTTTTA	139	2641
876956	N/A	N/A	53309	53328	ATAAATGGTGAATAACCATG	60	2642
876980	N/A	N/A	56543	56562	TGGATAACACCTAAAGGACC	122	2643
877004	N/A	N/A	59276	59295	GTATTTGGAGCAGTGCCCAG	110	2644
877028	N/A	N/A	61596	61615	GTACCTTAACACAGTAAATA	82	2645
877052	N/A	N/A	63476	63495	TAATCTACTATGTGCAAAAC	100	2646
877076	N/A	N/A	66557	66576	TCTACATTGTCAGGAAGCAA	66	2647
877100	N/A	N/A	68445	68464	ATCTCTCACAGATGCAAAAT	82	2648
877124	N/A	N/A	71781	71800	ATAATCACAATTGCACAATT	109	2649
877148	N/A	N/A	73144	73163	GAATCATTAGGTAAATATAT	99	2650
877172	N/A	N/A	74948	74967	AGTGGAGAAGAGAGAAAGAC	92	2651
877196	N/A	N/A	77137	77156	TATCAAAAACAATTTGCTTT	136	2652
877220	N/A	N/A	79895	79914	ACAGTCTCTTTTCTTATCTG	76	2653
877232	N/A	N/A	81609	81628	TTTAGTGTCAATTCTAAAAA	119	2654
877251	N/A	N/A	84464	84483	CAGTAGCTATAATGCTTTAA	80	2655
877275	N/A	N/A	87627	87646	TTTAGATTTCATTTAAGAAA	105	2656
877299	N/A	N/A	89982	90001	AATTACATGTCCAACAAGAG	92	2657
877323	N/A	N/A	91362	91381	AATAAAAGTATCTTCCAAAC	91	2658
877347	N/A	N/A	93509	93528	AAATTCACAAAAGTTTCTGC	80	2659
877371	N/A	N/A	95698	95717	TTTCATATCTCTTTTATCAT	97	2660
877395	N/A	N/A	97239	97258	TTTTGCTTTGTCAAATTCAC	45	2661
877419	N/A	N/A	100725	100744	CTATAATTGAATATACTATT	108	2662
877443	N/A	N/A	102592	102611	ATTAAATCAATCTAATGCAT	105	2663
877467	N/A	N/A	105313	105332	CTCAATCCCCAAGGAGTTTG	60	2664
877491	N/A	N/A	107115	107134	CTTTCACCCTGAACACACAG	68	2665
877515	N/A	N/A	110361	110380	CTCAACCCTCACCCATGCAG	93	2666
877539	N/A	N/A	112217	112236	CCTGCTTATAATCTCTGGTT	87	2667
877563	N/A	N/A	114595	114614	TCTGAAGGCTTACTATTTTA	71	2668
877587	N/A	N/A	117410	117429	ACTACAGCATTTCATGTGAT	46	2669
877611	N/A	N/A	119355	119374	ATGTATAGCCACCTGTAATT	93	2670
877635	N/A	N/A	121814	121833	CTTGGATAATTATCATAATG	41	2671
877659	N/A	N/A	124271	124290	TCTCTTGGGTTCATGCCTGA	67	2672
877683	N/A	N/A	127120	127139	TAAATATTTTTGTAGCTCTA	83	2673
877707	N/A	N/A	130019	130038	TGTTTCTAGGGACCCTGAGC	58	2674
877731	N/A	N/A	134194	134213	AAATGTTGAAATTGTTACAA	150	2675
877755	N/A	N/A	138536	138555	AAATGACAATTAGGAGGGTC	78	2676
877779	N/A	N/A	141131	141150	CTTGCAAAACTTTGTTTCAT	66	2677
877803	N/A	N/A	143288	143307	AATTTATACCAGTCTTATGT	126	2678
877827	N/A	N/A	144888	144907	ATTCTTAATTATGTGAGTCT	77	2679

표 42

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

[0656]

[0657]

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	35	222
803640	N/A	N/A	81631 87888	81650 87907	TGCAGCATCATGCAAGCAGC	22	1802
876022	547	566	N/A	N/A	TGATTTTACCTGAAGTTAGG	82	3134
876046	832	851	21663	21682	TCATGAGGACTTCCACATTA	50	3135
876070	1231	1250	29582	29601	GATTATTTAGTGCCCAGCAT	47	3136
876094	1475	1494	35422	35441	ACTTCAGGAGAATGTATATG	58	3137
876118	1683	1702	41916	41935	ATGAAATTCTGTATCCTCCC	70	3138
876142	2306	2325	56314	56333	GCATCTGCTCCCAATAGAAG	48	3139
876166	2871	2890	71714	71733	CTGTAATACGGCATCTCGGT	25	3140
876190	3231	3250	76365	76384	GTGCAAGTCCAAATGTGTCA	15	3141
876214	3803	3822	82148	82167	ATGCTGATCTGATTATGGCT	76	3142
876238	4190	4209	86685	86704	CCAAGATCTGATTTCTTGGT	72	139
876262	4728	4747	92151	92170	TGGCACATTTTTACGCTCCG	26	3143
876286	5049	5068	98197	98216	ATACTGTGACATGTAGTTCT	24	3144
876310	5429	5448	N/A	N/A	AGAATACAGCCTTTTCTACA	53	3145
876334	5655	5674	101293	101312	TGGAATGGTGAGCCTTGGTT	41	3146
876358	6249	6268	124880	124899	AATGACATTTCCTCTGGCAA	69	3147
876382	6870	6889	132580	132599	TTGCTTGGAAAAGGAATTGC	63	3148
876406	7747	7766	145916	145935	AATAAATATTTACAAGAGGA	165	3149
876430	8774	8793	146943	146962	GCTATGTAAACAATTTAAGT	96	3150
876454	N/A	N/A	4075	4094	ATTGGGAAGATACTTGGAAT	86	3151
876478	N/A	N/A	6864	6883	ACACAAATCATTTCAAAATG	80	3152
876502	N/A	N/A	8430	8449	GGCACAAGTTTCTTACTCGC	56	3153
876526	N/A	N/A	11515	11534	TCTAATTTGTCTAAATTTAT	120	3154
876550	N/A	N/A	14441	14460	CTCTGCACTTCAGTGTTTGT	55	3155
876574	N/A	N/A	16653	16672	ATCTCAGTTATCAATCTCAG	51	3156
876598	N/A	N/A	19231	19250	ATAACCCCACACCTTTACTG	239	3157
876622	N/A	N/A	20813	20832	CGAGGCTCAACCCCATTGGA	58	3158
876646	N/A	N/A	23976	23995	TATATAATTGCTAGGTAGAG	52	3159
876670	N/A	N/A	26660	26679	TCATTCAGCTACTTTTGAAA	55	3160
876694	N/A	N/A	29232	29251	ACCAACAGAATGAGGTGTGC	36	3161
876718	N/A	N/A	30990	31009	ATTCAAACAAAATGTTAGTA	125	3162
876742	N/A	N/A	33417	33436	ACTCAATAGTCACCTTCTTT	60	3163
876766	N/A	N/A	34874	34893	ATGTGGAGGTATCGACCATT	32	3164
876790	N/A	N/A	37365	37384	CGGGAATTATTTCACTTCAT	21	3165
876814	N/A	N/A	38809	38828	CCTTGTATCTAGTCTCTCTC	49	3166
876838	N/A	N/A	41299	41318	CTACAAGTCAAAAATGTGGT	71	3167
876862	N/A	N/A	43081	43100	ATCATTTCCATTAATTATTT	72	3168
876886	N/A	N/A	47247	47266	CTTAGAATGAAATTGCTGAT	48	3169
876910	N/A	N/A	48381	48400	TGCCAATGTGGAGTTAATTT	103	3170
876934	N/A	N/A	50807	50826	TAATTATTCTCAGTCTTTAA	110	3171

876958	N/A	N/A	53342	53361	TCTTAGCACATTCTCTGAAC	61	3172
876982	N/A	N/A	56609	56628	GACACATTTGAAAAGTTATT	45	3173
877006	N/A	N/A	59726	59745	TCTTTAGAATATTCACACAT	112	3174
877030	N/A	N/A	61906	61925	ACTGGCAAATCAAACTTCAT	104	3175
877054	N/A	N/A	63890	63909	AATGTAATCTTTATCAGGAC	65	3176
877078	N/A	N/A	66625	66644	TTGGAAAACAGACACAAAAG	61	3177
877102	N/A	N/A	68600	68619	GGCCTTTGCTGGTGAAGTCT	39	3178
877126	N/A	N/A	71855	71874	GAAATCCCTACCAATTGTTC	119	3179
877150	N/A	N/A	73433	73452	CAATCAGGCTTTCTTCAAGG	88	3180
877174	N/A	N/A	75007	75026	TGATGAAGTGACAGTTAAAT	116	3181
877198	N/A	N/A	77396	77415	GTACAACTTAGAGGGCCTGG	38	3182
877222	N/A	N/A	80337	80356	AGTTCTCAATACTCTGGTAT	35	3183
877253	N/A	N/A	84478	84497	ATTTCACATGATGTCAGTAG	61	3184
877277	N/A	N/A	87800	87819	AGATAGAAAAGCAACAAAAG	153	3185
877301	N/A	N/A	90174	90193	CAACAAGTCTTTTTAAAGAT	74	3186
877325	N/A	N/A	91493	91512	AACATCAGTGATTCTGATAG	136	3187
877349	N/A	N/A	93656	93675	GGATCTAGTAAAGCAGCATG	39	3188
877373	N/A	N/A	95702	95721	TCTCTTTCATATCTCTTTTA	42	3189
877397	N/A	N/A	97648	97667	GAATAGGAAGACAGACTGTG	69	3190
877421	N/A	N/A	100889	100908	TCTTTATAACAGTTCTATGA	99	3191
877445	N/A	N/A	102737	102756	GACAACTTTTTGCTAATAAT	70	3192
877469	N/A	N/A	105355	105374	TTCAGGCCTCCATACCCTTG	184	3193
877493	N/A	N/A	107755	107774	AGAGAATCCATTTGACTTTG	37	3194
877517	N/A	N/A	110432	110451	GAATACAGGAATAACCACTG	61	3195
877541	N/A	N/A	112355	112374	AACAGTGCACACAGTGTAGT	46	3196
877565	N/A	N/A	114614	114633	CTACTGTCAACACAGTAATT	72	3197
877589	N/A	N/A	117436	117455	CTTCTCTGCCCCATGATGTC	56	3198
877613	N/A	N/A	119406	119425	TTTCTTCTGTGCCAGGCACG	47	3199
877637	N/A	N/A	121914	121933	GCCACTATTAAGTGGTAGAG	52	3200
877661	N/A	N/A	124653	124672	CCAAGGTTGACCACACAGGA	66	3201
877685	N/A	N/A	127508	127527	TCATAAGATTTGACAGCATG	48	3202
877709	N/A	N/A	130133	130152	TTCAGAAACCACATTTCTGC	123	3203
877733	N/A	N/A	134456	134475	CAATCAGCAAGTATTTTCAG	113	3204
877757	N/A	N/A	138991	139010	GTGGTGCTTGGACTGAAATA	85	3205
877781	N/A	N/A	141186	141205	TTGTACTATATCTAAATTTC	89	3206
877805	N/A	N/A	143353	143372	TAATCTGCTTCTCTTGTGGG	71	3207
877829	N/A	N/A	145054	145073	ATATTAAACTGGCCTGAAAA	145	3208

[0658]

표 43

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호

780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	49	222
803641	N/A	N/A	81632 87889	81651 87908	TTGCAGCATCATGCAAGCAG	57	1803
876023	662	681	16182	16201	AGCACATGTAAAGCTTTGCA	51	3209
876047	833	852	21664	21683	CTCATGAGGACTTCCACATT	60	3210
876071	1232	1251	29583	29602	AGATTATTTAGTGCCCAGCA	43	3211
876095	1476	1495	35423	35442	CACTTCAGGAGAATGTATAT	35	3212
876119	1694	1713	41927	41946	TTTAGCTTATGATGAAATTC	36	3213
876143	2395	2414	62016	62035	CACTATTCAGTAAGAGTTCC	19	3214
876167	2873	2892	71716	71735	CGCTGTAATACGGCATCTCG	58	3215
876191	3250	3269	76384	76403	ATGATGTAAATTTATTACTG	75	3216
876215	3804	3823	82149	82168	GATGCTGATCTGATTATGGC	33	3217
876239	4232	4251	86727	86746	GGCCAGTCTTTCACATCTAT	39	3218
876263	4729	4748	92152	92171	TTGGCACATTTTTACGCTCC	21	3219
876287	5050	5069	98198	98217	AATACTGTGACATGTAGTTC	38	3220
876311	5434	5453	N/A	N/A	CCAAAAGAATACAGCCTTTT	52	3221
876335	5660	5679	101298	101317	GATATTGGAATGGTGAGCCT	28	3222
876359	6288	6307	124919	124938	TAGTAAACCAAATGAATAAA	78	3223
876383	6953	6972	N/A	N/A	CCTTTAAGCTTAACAGTCTT	125	3224
876407	7856	7875	146025	146044	TTACTGGTAAGTATTTTTAC	57	3225
876431	8779	8798	146948	146967	GGTAAGCTATGTAAACAATT	105	3226
876455	N/A	N/A	4112	4131	AACTATTCATAATCTTCTCA	93	3227
876479	N/A	N/A	6910	6929	TTGGCTGTGCAAAAGAAGGA	112	3228
876503	N/A	N/A	8563	8582	CTGCTACATGATAAGGAAGC	62	3229
876527	N/A	N/A	11614	11633	CACACCCTTTATGTACTGAA	33	3230
876551	N/A	N/A	14462	14481	TCTTAGTGGCCAAAGCAACT	80	3231
876575	N/A	N/A	16768	16787	TCACAAGCTCTGTGTCCTCA	45	3232
876599	N/A	N/A	19233	19252	TCATAACCCCACACCTTTAC	91	3233
876623	N/A	N/A	20902	20921	TTTTTTTTGATGTGGAGAAA	161	3234
876647	N/A	N/A	24058	24077	GACTCATGTAAGAAGACAAG	48	3235
876671	N/A	N/A	26694	26713	TTTAATTTTAACTATGAAGA	101	3236
876695	N/A	N/A	29272	29291	TAACAGTTTGACCAACTCTA	76	3237
876719	N/A	N/A	30991	31010	AATTCAAACAAAATGTTAGT	180	3238
876743	N/A	N/A	33419	33438	TTACTCAATAGTCACCTTCT	62	3239
876767	N/A	N/A	34973	34992	TTCCAATACTTAAAACAAGT	76	3240
876791	N/A	N/A	37386	37405	AAGATAGAATTCATAGTAAT	108	3241
876815	N/A	N/A	38831	38850	CCATGGACCTCCAACCCAAT	86	3242
876839	N/A	N/A	41301	41320	CACTACAAGTCAAAAATGTG	62	3243
876863	N/A	N/A	43157	43176	ATTTTTAAGGGAGATCTCTC	56	3244
876887	N/A	N/A	47300	47319	TTCATGTCTAATAATCTTTA	64	3245
876911	N/A	N/A	48530	48549	TCTAAAGAAATTCAGACAAC	115	3246
876935	N/A	N/A	50878	50897	CAAAGAAAAAAGTCCAATAA	168	3247
876959	N/A	N/A	53439	53458	GCAACCTGCAATAAAACCCA	43	3248
876983	N/A	N/A	56638	56657	AGACTAAGTTGTAGAGATGC	79	3249
877007	N/A	N/A	59787	59806	TAAAATAAATAAATGCCAGC	125	3250
877031	N/A	N/A	62296	62315	ACTAAAAGACTAGTGACTTA	69	3251
877055	N/A	N/A	64013	64032	GAACCCATTTCTGGAGGGTT	180	3252
877079	N/A	N/A	66732	66751	CACTAGAACAGCTAAAAGTA	172	3253

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877103	N/A	N/A	68807	68826	TCACTAACAGGATAATTAAA	103	3254
877127	N/A	N/A	72021	72040	TGAAGTGTACTGTAAGTATA	46	3255
877151	N/A	N/A	73765	73784	CTTGAAAGTTACAAGGATAA	60	3256
877175	N/A	N/A	75058	75077	GGTGGGTAGGTTGGCTGGAG	88	3257
877199	N/A	N/A	77450	77469	ACTGAAATGCCACTTTTAAA	74	3258
877223	N/A	N/A	80422	80441	ATGGGTGTTATTTAATAAAA	65	3259
877254	N/A	N/A	84582	84601	AAGTGTAAAGACCAGAAACA	169	3260
877278	N/A	N/A	87864	87883	TAGTCTCCATTCTAAAAAGC	64	3261
877302	N/A	N/A	90291	90310	GACTTATTGGTAATGATATC	57	3262
877326	N/A	N/A	91566	91585	GCAGAGACATAAAATCCCAC	36	3263
877350	N/A	N/A	93891	93910	TTCCATGTGAAATATAAGAA	79	3264
877374	N/A	N/A	95756	95775	AAGGTTAAATTGCCATGTAA	45	3265
877398	N/A	N/A	97666	97685	CTAGGAGAGGACTTCCATGA	52	3266
877422	N/A	N/A	100940	100959	ATTATATGGCAGACATGTTG	73	3267
877446	N/A	N/A	102740	102759	TTGGACAACTTTTTGCTAAT	72	3268
877470	N/A	N/A	105358	105377	ACCTTCAGGCCTCCATACCC	95	3269
877494	N/A	N/A	107793	107812	CCTTTATTTTTATAAATTGA	51	3270
877518	N/A	N/A	110571	110590	TACAGTTGAGTTCTGGTATA	100	3271
877542	N/A	N/A	112357	112376	GAAACAGTGCACACAGTGTA	56	3272
877566	N/A	N/A	114956	114975	AAAAACTAGAACCTAGAGTT	90	3273
877590	N/A	N/A	117469	117488	AGATGTCTATAAAATTCTGA	77	3274
877614	N/A	N/A	119511	119530	AACCAGGCATTGGAATCTGG	65	3275
877638	N/A	N/A	121934	121953	AATTTCTTGATGAACATCAT	69	3276
877662	N/A	N/A	124733	124752	CTAAACCAGGCTGTGTTATT	75	3277
877686	N/A	N/A	127511	127530	TTTTCATAAGATTTGACAGC	83	3278
877710	N/A	N/A	130554	130573	TTTAACCTCAGAACTAATGT	152	3279
877734	N/A	N/A	134509	134528	ATCAGATGTCATTTATCATT	67	3280
877758	N/A	N/A	139025	139044	AGCACAAAGTCACCTAACCT	50	3281
877782	N/A	N/A	141209	141228	TCTATGTGGCTCTTTGTAGA	50	3282
877806	N/A	N/A	143361	143380	AGCTGCAGTAATCTGCTTCT	33	3283
877830	N/A	N/A	145056	145075	ATATATTAAACTGGCCTGAA	152	3284

표 44

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	23	222
780625	N/A	N/A	81633	81652	ATTGCAGCATCATGCAAGCA	56	675
			87890	87909			
876024	667	686	16187	16206	CAAACAGCACATGTAAAGCT	75	3285
876048	834	853	21665	21684	ACTCATGAGGACTTCCACAT	42	3286

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[0661]

876072	1233	1252	29584	29603	GAGATTATTTAGTGCCCAGC	30	3287
876096	1477	1496	35424	35443	CCACTTCAGGAGAATGTATA	48	3288
876120	1696	1715	41929	41948	TATTTAGCTTATGATGAAAT	58	3289
876144	2400	2419	62021	62040	AGATCCACTATTCAGTAAGA	42	3290
876168	2874	2893	71717	71736	ACGCTGTAATACGGCATCTC	26	3291
876192	3289	3308	76423	76442	GATTAGCAATACAACTCATT	41	3292
876216	3805	3824	82150	82169	AGATGCTGATCTGATTATGG	46	3293
876240	4237	4256	86732	86751	GGATAGGCCAGTCTTTCACA	43	3294
876264	4731	4750	92154	92173	AATTGGCACATTTTTACGCT	41	3295
876288	5052	5071	98200	98219	AAAATACTGTGACATGTAGT	26	3296
876312	5444	5463	100433	100452	ACAACTTGGCCCAAAAGAAT	101	3297
876336	5690	5709	101328	101347	TCAGCCAAAATCAAGTCAGG	50	3298
876360	6293	6312	124924	124943	TAGAGTAGTAAACCAAATGA	82	3299
876384	6958	6977	N/A	N/A	CAGCTCCTTTAAGCTTAACA	73	3300
876408	7861	7880	146030	146049	CACATTTACTGGTAAGTATT	52	3301
876432	8818	8837	146987	147006	AATTATTACATAGGTATTTG	97	3302
876456	N/A	N/A	4226	4245	GGTATACTACAACTAAAGGC	45	3303
876480	N/A	N/A	6916	6935	CAAATATTGGCTGTGCAAAA	50	3304
876504	N/A	N/A	8607	8626	TAAGCCAGATTGTATAAGAA	91	3305
876528	N/A	N/A	11615	11634	ACACACCCTTTATGTACTGA	35	3306
876552	N/A	N/A	14467	14486	CTACCTCTTAGTGGCCAAAG	58	3307
876576	N/A	N/A	16784	16803	TAATTGAACTGTACTGTCAC	77	3308
876600	N/A	N/A	19236	19255	CACTCATAACCCCACACCTT	68	3309
876624	N/A	N/A	20923	20942	TGTTATATTGCTTACCTTTT	69	3310
876648	N/A	N/A	24093	24112	TCAATGGCTCTATTTAACAC	74	3311
876672	N/A	N/A	26696	26715	GTTTTAATTTTAACTATGAA	63	3312
876696	N/A	N/A	29292	29311	CATTATATATATTATCTACT	94	3313
876720	N/A	N/A	30992	31011	AAATTCAAACAAAATGTTAG	77	3314
876744	N/A	N/A	33420	33439	CTTACTCAATAGTCACCTTC	51	3315
876768	N/A	N/A	35168	35187	ACACATGTCATTTCCAATTT	38	3316
876792	N/A	N/A	37410	37429	TAATTGTCTAAACTTTGAAC	72	3317
876816	N/A	N/A	38923	38942	TCACATCAAACAGATCTCCC	68	3318
876840	N/A	N/A	41323	41342	TGTAGCTGAACTATGCTAAA	118	3319
876864	N/A	N/A	43234	43253	TGTATTAAAGTTTGAGTATA	77	3320
876888	N/A	N/A	47312	47331	CCACAGTGAACATTCATGTC	39	3321
876912	N/A	N/A	48595	48614	GTCCAAATATAAAGGCAAAA	36	3322
876936	N/A	N/A	51297	51316	AGAAGTGGTAAGTTAAAAAG	101	3323
876960	N/A	N/A	53567	53586	CCAGTATCTTGAATTCCTTA	38	3324
876984	N/A	N/A	56680	56699	TATCAAAACATTAGAACTAT	86	3325
877008	N/A	N/A	59803	59822	GAGAAAGTGAATCTGATAAA	48	3326
877032	N/A	N/A	62335	62354	ATCTTTGGCTTAAGGTCCCT	54	3327
877056	N/A	N/A	64117	64136	TGAAGATTAAAGTAAGCAGG	46	3328
877080	N/A	N/A	66821	66840	AATAAGAATGGCCAATAAGA	97	3329
877104	N/A	N/A	68820	68839	CAGGATAATTAAATCACTAA	89	3330
877128	N/A	N/A	72024	72043	TCTTGAAGTGTACTGTAAGT	36	3331
877152	N/A	N/A	73771	73790	AAATGTCTTGAAAGTTACAA	58	3332
877176	N/A	N/A	75109	75128	ACCGAATGAGAATTAGGTGG	22	3333
877200	N/A	N/A	77633	77652	ATAATTTTGTCTCTTCCAGA	61	3334

877224	N/A	N/A	80461	80480	TATGGTACTAGCTCATAAAG	87	3335
877255	N/A	N/A	84665	84684	TATGAGAAAGTAATAAGACC	103	3336
877279	N/A	N/A	87867	87886	GTTTAGTCTCCATTCTAAAA	58	3337
877303	N/A	N/A	90326	90345	AGGTGATTTATAAGTGCCAA	28	3338
877327	N/A	N/A	91617	91636	GGTTATTTGTAAAATGTTAT	33	3339
877351	N/A	N/A	93895	93914	CATTTTCCATGTGAAATATA	50	3340
877375	N/A	N/A	95790	95809	AAATTCCTTTGTATTTCTCC	31	3341
877399	N/A	N/A	97756	97775	GTCTCATCAATAATATATTC	46	3342
877423	N/A	N/A	100944	100963	TGTTATTATATGGCAGACAT	66	3343
877447	N/A	N/A	102748	102767	CTCAAATTTTGGACAACTTT	66	3344
877471	N/A	N/A	105367	105386	ATGCTTTGTACCTTCAGGCC	39	3345
877495	N/A	N/A	108045	108064	TTAGAAACACTTGAAGTCAT	61	3346
877519	N/A	N/A	110743	110762	AATTAAAATGCCCCCAGGAT	74	3347
877543	N/A	N/A	112384	112403	CTCTGTTTTTATCAGACATT	49	3348
877567	N/A	N/A	115086	115105	GTTATTTAAAGTAAGGTTTC	52	3349
877591	N/A	N/A	117552	117571	TTCATCTCAACCAGGTCTTA	67	3350
877615	N/A	N/A	119913	119932	AGTTGCATATGGTTTAGGAG	29	3351
877639	N/A	N/A	122135	122154	AATATTTACTTCAATATGGA	68	3352
877663	N/A	N/A	124792	124811	CATCCAAGGAGGCATACACT	78	3353
877687	N/A	N/A	127780	127799	TTAAAGGAAAAGTTAACCAG	75	3354
877711	N/A	N/A	132127	132146	GATTGTTCCTCTCCCTCTCC	57	3355
877735	N/A	N/A	134694	134713	TAATGACTAAATAGGAATCT	89	3356
877759	N/A	N/A	139104	139123	GTAGATTTAGTGGTATTGAG	54	3357
877783	N/A	N/A	141286	141305	ACTTTATATTAATTTCTTGT	67	3358
877807	N/A	N/A	143430	143449	TACCATGTATTTCCCATTTT	61	3359
877831	N/A	N/A	145069	145088	TTCTGTTAAAACTATATATT	128	3360

표 45

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	16	222
876028	732	751	18631	18650	ACTTAACAATATCATATAAT	116	3361
876052	840	859	21671	21690	ATTGCCACTCATGAGGACTT	23	3362
876076	1239	1258	29590	29609	CATAAGGAGATTATTTAGTG	51	3363
876100	1482	1501	35429	35448	TTCAGCCACTTCAGGAGAAT	36	3364
876124	1701	1720	41934	41953	AACCATATTTAGCTTATGAT	35	3365
876148	2452	2471	62073	62092	TGTCACCTTTCCCAATGCTT	37	3366
876172	2977	2996	73001	73020	GTGAATCATCTGAAGATAAT	79	3367
876196	3422	3441	76556	76575	TCTACCACATCAGTGAGGTT	46	3368
876220	3850	3869	82195	82214	GTTTCTCTACTCTAGACCAT	29	3369

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876244	4313	4332	87217	87236	GTACTATAGAATTCCTCACG	33	3370
876268	4736	4755	92159	92178	AATTCAATTGGCACATTTTT	80	3371
876292	5070	5089	98218	98237	GAATTTTTCTAGGAGCTTAA	47	3372
876316	5450	5469	100439	100458	TGGTCCACAACTTGGCCCAA	45	3373
876340	5704	5723	101342	101361	TATTTCTAGGCAGGTCAGCC	62	3374
876364	6471	6490	126587	126606	AGGCCTTTCTTGAGGATTTT	56	3375
876388	7076	7095	137480	137499	GAGAAAATCTTTGTGCCACA	66	3376
876412	8045	8064	146214	146233	ACAGAATTTAAAATAAAGTT	64	3377
876436	8906	8925	147075	147094	TATCACAGGGAATTATCTGA	113	3378
876460	N/A	N/A	4437	4456	ATCACCTTGGCCTATAATTT	73	3379
876484	N/A	N/A	7124	7143	TTGCTTTTTACTAGCTTGCA	38	3380
876508	N/A	N/A	9022	9041	GGCTCTTTCACATTTCGAAA	63	3381
876532	N/A	N/A	11902	11921	TTTCCTACATAAACTTTTAT	137	3382
876556	N/A	N/A	14858	14877	GTTGAGTACCTTCTTGTTTT	43	3383
876580	N/A	N/A	17001	17020	TCTTGTGTATTATAATTATC	55	3384
876604	N/A	N/A	19521	19540	AGCAATCATTGGTAGCATAC	17	3385
876628	N/A	N/A	21334	21353	GTACTGAAAATGAAAGTCTG	79	3386
876652	N/A	N/A	24857	24876	AAGGTAAGGTCTCAACCAGA	41	3387
876676	N/A	N/A	27470	27489	TCATTGGCATGTTTACCATT	46	3388
876700	N/A	N/A	29725	29744	CTAACAATAAAAGTTACGGT	49	3389
876724	N/A	N/A	31409	31428	AATTTGGTTATAAAAGAGTA	94	3390
876748	N/A	N/A	33425	33444	CAGGTCTTACTCAATAGTCA	32	3391
876772	N/A	N/A	35704	35723	AGCATCAGGTTCAAAAGCAA	43	3392
876796	N/A	N/A	37927	37946	CATTGTAGTTACTTTGTATA	100	3393
876820	N/A	N/A	39204	39223	AAACTATGAATAGGACACCA	49	3394
876844	N/A	N/A	41563	41582	CTGGAAGATTTTTATGCAAC	66	3395
876868	N/A	N/A	45405	45424	CTCTCACAATGAGACAGGAT	48	3396
876892	N/A	N/A	47401	47420	GGTGGAGAAATAAAAATATC	153	3397
876916	N/A	N/A	49326	49345	GATGTCCCTTGTCTATGAGT	80	3398
876940	N/A	N/A	51672	51691	GTCTTTGACCAAAATCTTCT	53	3399
876964	N/A	N/A	54224	54243	CTATCTTGGTTTAATCAGCC	51	3400
876988	N/A	N/A	57012	57031	ATATATTTTCATAGACTGAC	73	3401
877012	N/A	N/A	59950	59969	CATCTTGAAACAGGAAACCC	90	3402
877036	N/A	N/A	62729	62748	GCTTGAAAGTATAAAGAAAA	92	3403
877060	N/A	N/A	64985	65004	GCTAAATAAAGGATCTTGTT	61	3404
877084	N/A	N/A	67063	67082	TCTTAAGTGGGATACAAAAA	77	3405
877108	N/A	N/A	69905	69924	AATTACAACTTCAATATTTC	117	3406
877132	N/A	N/A	72455	72474	CAAAGTGAACCTGAGAATAA	86	3407
877156	N/A	N/A	73937	73956	TCTGTTTCCATTGCCTGCCC	24	3408
877180	N/A	N/A	75325	75344	ATTATTTTGCTTGCTCATTT	62	3409
877204	N/A	N/A	78164	78183	TATCTCAGTATCAGGATGCC	36	3410
877228	N/A	N/A	81375	81394	TACATAAACTTGCCTAATCT	120	3411
877235	N/A	N/A	82381	82400	ATGGAAATCTGGATTTATAG	48	3412
877259	N/A	N/A	84939	84958	TCAGAAAACAAAATCCTTCC	70	3413
877283	N/A	N/A	87993	88012	CATTAAAAAATACCCAAATT	142	3414
877307	N/A	N/A	90438	90457	TCAAACCATTATGCCAGAAT	34	3415
877331	N/A	N/A	91722	91741	AATGTGAAACAGACACGCTA	53	3416
877355	N/A	N/A	94450	94469	AATGTTTCAATATGCTCTTG	22	3417

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877379	N/A	N/A	95946	95965	ATTTTAAGCCTCCAAGTTTC	110	3418
877403	N/A	N/A	98420	98439	CAAAATAAATGATACATGTC	104	3419
877427	N/A	N/A	101435	101454	CATCCTAATTTTTATTCTCA	94	3420
877451	N/A	N/A	103549	103568	AGCCAAAATGGCAACAGCTC	52	3421
877475	N/A	N/A	105747	105766	TCATTCCACTTTGATTGTGT	40	3422
877499	N/A	N/A	108438	108457	GGAATTTTCTTCAAATTTTG	102	3423
877523	N/A	N/A	111233	111252	TCATAGGCACAGACAGAGGT	68	3424
877547	N/A	N/A	112873	112892	ACTACAGTTGACCTATGGAC	74	3425
877571	N/A	N/A	115802	115821	ATTGCAAGCATAAACAGATT	98	3426
877595	N/A	N/A	118045	118064	ATGAATATTTTAACTATTTC	65	3427
877619	N/A	N/A	119984	120003	GCTATTCATGGCTCTGTTGT	66	3428
877643	N/A	N/A	122352	122371	GTTAGAATTTGGAATCACAG	42	3429
877667	N/A	N/A	125287	125306	CAAATGTGGAGTTCTAACAG	106	3430
877691	N/A	N/A	128589	128608	TGGACAAGGTTACTTGGGCA	55	3431
877715	N/A	N/A	132782	132801	TTTATAAATGTCTCAGCTAG	72	3432
877739	N/A	N/A	135635	135654	ATTGCTATAGCCACTACGGA	102	3433
877763	N/A	N/A	140038	140057	CTAGAACTCCAAAAGTCCTA	76	3434
877787	N/A	N/A	141378	141397	ACAAGCTAGACTATTGCAAT	55	3435
877811	N/A	N/A	143863	143882	GAATATATTTTCTTCACCAT	62	3436
877835	N/A	N/A	145294	145313	AAACTACCAATTAAAATTCC	80	3437

표 46

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	42	222
876029	733	752	18632	18651	CACTTAACAATATCATATAA	73	3438
876053	841	860	21672	21691	CATTGCCACTCATGAGGACT	29	3439
876077	1249	1268	29600	29619	TGTTTTGGTACATAAGGAGA	60	3440
876101	1483	1502	35430	35449	TTTCAGCCACTTCAGGAGAA	50	3441
876125	1702	1721	41935	41954	TAACCATATTTAGCTTATGA	56	3442
876149	2453	2472	62074	62093	CTGTCACCTTTCCCAATGCT	26	3443
876173	3064	3083	73600	73619	CTAGTGATGTAATATATTCT	32	3444
876197	3427	3446	76561	76580	GTTTCTCTACCACATCAGTG	38	3445
876221	3852	3871	82197	82216	CAGTTTCTCTACTCTAGACC	28	3446
876245	4315	4334	87219	87238	GAGTACTATAGAATTCCTCA	81	3447
876269	4741	4760	92164	92183	CGGGAAATTCAATTGGCACA	44	3448
876293	5071	5090	98219	98238	GGAATTTTTCTAGGAGCTTA	27	3449
876317	5451	5470	100440	100459	GTGGTCCACAACTTGGCCCA	72	152
876341	5745	5764	101383	101402	TGGAGCTTGTTCAAATTCCA	52	153
876365	6510	6529	129655	129674	TTCAGCTGAATTCAAAATGT	82	3450

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876389	7174	7193	141535	141554	CCACTGTTATGATGTTGGAA	65	3451
876413	8085	8104	146254	146273	ATTTCTAGAAAAATCGACAA	115	3452
876437	8911	8930	147080	147099	TGTCCTATCACAGGGAATTA	81	3453
876461	N/A	N/A	4590	4609	GTCTGTCAAGCCTCTCAACC	79	3454
876485	N/A	N/A	7136	7155	TATCAAACCATTTTGCTTTT	79	3455
876509	N/A	N/A	9076	9095	CAGATTTCTCTAGAATGAAT	67	3456
876533	N/A	N/A	12031	12050	TGTGTCTATCTTCTTCACAA	119	3457
876557	N/A	N/A	14909	14928	AGACTCTTAGTGCATGCCAT	46	3458
876581	N/A	N/A	17076	17095	CCTTAGAAACACAGTAAACT	72	3459
876605	N/A	N/A	19554	19573	AAAACAGAATATGAACCATT	48	3460
			19584	19603			
876629	N/A	N/A	21340	21359	GGAAAAGTACTGAAAATGAA	134	3461
876653	N/A	N/A	24869	24888	CAGACTCTCTGCAAGGTAAG	88	3462
876677	N/A	N/A	27495	27514	CTTAAAGGAATAGTGCTTAG	71	3463
876701	N/A	N/A	29875	29894	AATTACCAAATGACCCTTGA	73	3464
876725	N/A	N/A	31897	31916	TGGTGTTTACTATGGGTTCC	28	3465
876749	N/A	N/A	33427	33446	TGCAGGTCTTACTCAATAGT	75	3466
876773	N/A	N/A	35778	35797	CACACAATAATTAGAAAAAC	106	3467
876797	N/A	N/A	37999	38018	TCATGGCAACAAAAATAGAA	129	3468
876821	N/A	N/A	39337	39356	TGTCAACTTTAAGGATAATC	35	3469
876845	N/A	N/A	41680	41699	TAAATATAATGTGTAAGAAT	117	3470
876869	N/A	N/A	45530	45549	CACCAACACTCACCATGAAT	62	3471
876893	N/A	N/A	47579	47598	CCCTCAGGGACCTCTACTGA	59	3472
876917	N/A	N/A	49662	49681	ATTTATCAGTGTCTACTTAG	68	3473
876941	N/A	N/A	51782	51801	TTCATTTAGATGATGTTTTG	95	3474
876965	N/A	N/A	54337	54356	ACTCTACTATAGAGATTCTA	95	3475
876989	N/A	N/A	57276	57295	ATTTAATAATGTGTATTAAA	129	3476
877013	N/A	N/A	59957	59976	TACAAACCATCTTGAAACAG	98	3477
877037	N/A	N/A	62733	62752	ATGAGCTTGAAAGTATAAAG	83	3478
877061	N/A	N/A	65104	65123	GTATCAGTGTCCTCACCTGG	84	3479
877085	N/A	N/A	67064	67083	TTCTTAAGTGGGATACAAAA	81	3480
877109	N/A	N/A	69996	70015	ATAGTCCTTAATGTTTGCAC	46	3481
877133	N/A	N/A	72458	72477	TTTCAAAGTGAACCTGAGAA	83	3482
877157	N/A	N/A	73938	73957	ATCTGTTTCCATTGCCTGCC	69	3483
877181	N/A	N/A	75378	75397	CCTTGTCACAGTCTCTTCCA	56	3484
877205	N/A	N/A	78262	78281	AAAACCATTAAATGATTAAT	148	3485
877229	N/A	N/A	81468	81487	AACACACTCAAGATCCAATT	94	3486
877236	N/A	N/A	82634	82653	ATCACACATAATTTGAAATG	91	3487
877260	N/A	N/A	85112	85131	AGTATAATACACTGAAAGCT	86	3488
877284	N/A	N/A	88019	88038	AGCTGTAAAAAAGTTAATAA	80	3489
877308	N/A	N/A	90441	90460	TTTTCAAACCATTATGCCAG	77	3490
877332	N/A	N/A	91728	91747	AAACTTAATGTGAAACAGAC	77	3491
877356	N/A	N/A	94452	94471	GCAATGTTTCAATATGCTCT	13	3492
877380	N/A	N/A	96049	96068	GAATGAAGCCAAGTGAATAA	82	3493
877404	N/A	N/A	98444	98463	AGTGTCAGATGCAATGTTTT	92	3494
877428	N/A	N/A	101447	101466	AGGAGAAAATTACATCCTAA	81	3495
877452	N/A	N/A	104028	104047	AAGAGGAAATGTACCCTGTG	77	3496
877476	N/A	N/A	105776	105795	CTCTCTCTCTTGCAAAATTA	74	3497

[0665]

877500	N/A	N/A	108554	108573	AATTCAAAAGGTCAAATTTT	105	3498
877524	N/A	N/A	111239	111258	TTGTTTTCATAGGCACAGAC	35	3499
877548	N/A	N/A	112899	112918	TTCAGTAATAAAAAGCTGGT	63	3500
877572	N/A	N/A	115808	115827	CAAGGAATTGCAAGCATAAA	69	3501
877596	N/A	N/A	118216	118235	GTCTAATATTACACAGCAAA	55	3502
877620	N/A	N/A	119990	120009	ATATTTGCTATTCATGGCTC	54	3503
877644	N/A	N/A	122379	122398	AGCATATTTTTTCTTGATAA	40	3504
877668	N/A	N/A	125297	125316	TAAAAATCACCAAATGTGGA	85	3505
877692	N/A	N/A	128599	128618	GATAATATGGTGGACAAGGT	38	3506
877716	N/A	N/A	132876	132895	GATTCATTGATCTGAGGAGA	55	3507
877740	N/A	N/A	135638	135657	TAAATTGCTATAGCCACTAC	72	3508
877764	N/A	N/A	140071	140090	TTGCCGACCTAGGACTAAAA	53	3509
877788	N/A	N/A	141480	141499	AAAAAATAGAAAGTCATCAC	128	3510
877812	N/A	N/A	143888	143907	TTCCTCTTTCACATATACTT	77	3511
877836	N/A	N/A	145295	145314	TAAACTACCAATTAAAATTC	139	3512

표 47

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	31	222
876030	734	753	18633	18652	GCACTTAACAATATCATATA	34	3513
876054	846	865	21677	21696	CCTGACATTGCCACTCATGA	38	3514
876078	1293	1312	N/A	N/A	AGCTGGGAAATGGCCATCTT	64	3515
876102	1484	1503	35431	35450	CTTTCAGCCACTTCAGGAGA	62	3516
876126	1704	1723	41937	41956	TTTAACCATATTTAGCTTAT	58	3517
876150	2454	2473	62075	62094	GCTGTCACCTTTCCCAATGC	31	3518
876174	3069	3088	73605	73624	AAGGTCTAGTGATGTAATAT	43	3519
876198	3457	3476	N/A	N/A	TTTTATTTCCTTCTAAAATG	113	3520
876222	3853	3872	82198	82217	GCAGTTTCTCTACTCTAGAC	25	3521
876246	4316	4335	87220	87239	TGAGTACTATAGAATTCCTC	46	3522
876270	4751	4770	92174	92193	CGGTCAATTACGGGAAATTC	45	3523
876294	5073	5092	98221	98240	CTGGAATTTTTCTAGGAGCT	13	3524
876318	5452	5471	100441	100460	TGTGGTCCACAACTTGGCCC	43	3525
876342	5787	5806	106478	106497	TCGGTAAACTGATCCAAAAC	63	3526
876366	6515	6534	129660	129679	ACTAATTCAGCTGAATTCAA	67	3527
876390	7179	7198	141540	141559	TACCACCACTGTTATGATGT	45	3528
876414	8090	8109	146259	146278	TGCAGATTTCTAGAAAAATC	43	3529
876438	8978	8997	147147	147166	TATAAATAAATTTAAAGTTT	96	3530
876462	N/A	N/A	4609	4628	AAAGATTGAGATGCCTCATG	73	3531
876486	N/A	N/A	7222	7241	GTAGGAGACCCCTTTCTACA	67	3532

[0666]

876510	N/A	N/A	9202	9221	AATGAAGCTAGAATAATAGA	118	3533
876534	N/A	N/A	12064	12083	GAGTGATCTAATACACTCCA	93	3534
876558	N/A	N/A	14962	14981	CCGTCAAAAAAAAAATACCT	129	3535
876582	N/A	N/A	17310	17329	CTCGCTGCAATACACTTTGT	66	3536
876606	N/A	N/A	19555	19574	CAAAACAGAATATGAACCAT	84	3537
			19585	19604			
876630	N/A	N/A	21645	21664	TATTGCCTGAATTTAAAGAG	81	3538
876654	N/A	N/A	25038	25057	ACTTTTAAATGCATTGTTGT	72	3539
876678	N/A	N/A	27571	27590	TTTAAAGTTGAAACTCTTAA	124	3540
876702	N/A	N/A	29941	29960	TGAATTAATATGGCATTTTA	86	3541
876726	N/A	N/A	31920	31939	AAACAGAGGAGGAAAGTGAT	126	3542
876750	N/A	N/A	33456	33475	TCAGAGGCAAAAAACAATAT	67	3543
876774	N/A	N/A	35835	35854	CGTTGTGAAAGAGCAAAATT	50	3544
876798	N/A	N/A	38037	38056	GTACAATTCAAACAAGAGAA	100	3545
876822	N/A	N/A	39461	39480	GAAATACTGTATTCAAAACT	73	3546
876846	N/A	N/A	41819	41838	GACTGTTACTTTCTAGAAAT	93	3547
876870	N/A	N/A	45583	45602	GGCTAACTGGAACCAGTTAT	48	3548
876894	N/A	N/A	47597	47616	GACTCTGCTTGTTGTAGTCC	68	3549
876918	N/A	N/A	49701	49720	TAATGTATTGCATTGGTGCT	62	3550
876942	N/A	N/A	51819	51838	TAAAAATTATAGTGCCATCC	51	3551
876966	N/A	N/A	54764	54783	AATGCTACAGCAGAGCAGGC	45	3552
876990	N/A	N/A	57307	57326	AACTATTGGCAAACATAGTA	76	3553
877014	N/A	N/A	59967	59986	CATACAGACCTACAAACCAT	69	3554
877038	N/A	N/A	62754	62773	CATAATATGTACAAAATACA	100	3555
877062	N/A	N/A	65304	65323	AGTGATCCTGAATAATTAAC	94	3556
877086	N/A	N/A	67065	67084	TTTCTTAAGTGGGATACAAA	66	3557
877110	N/A	N/A	70097	70116	AATTCTTCCAGAGGAAGAAA	123	3558
877134	N/A	N/A	72483	72502	ATTGGAGAATAGGTTAGAAC	64	3559
877158	N/A	N/A	73939	73958	GATCTGTTTCCATTGCCTGC	44	3560
877182	N/A	N/A	75408	75427	TGTCCAGTCATTGAATGCCG	30	3561
877206	N/A	N/A	78354	78373	CTTTTAATAAAAGTGATGAT	115	3562
877230	N/A	N/A	81470	81489	ACAACACACTCAAGATCCAA	68	3563
877237	N/A	N/A	82682	82701	AACAGTTAAGAATAATTTGA	122	3564
877261	N/A	N/A	85276	85295	CACTATTTGAAAAAATGTCT	81	3565
877285	N/A	N/A	88051	88070	GACTGCCACTGTACTATTTG	45	3566
877309	N/A	N/A	90454	90473	GCAATCAAATGAGTTTTCAA	66	3567
877333	N/A	N/A	92392	92411	ATCAGTGGCCTATTAAAGAA	98	3568
877357	N/A	N/A	94453	94472	TGCAATGTTTCAATATGCTC	34	3569
877381	N/A	N/A	96103	96122	CAATACTCCAAAAACATGCA	52	3570
877405	N/A	N/A	98870	98889	TTAGTTATGCATAGACAAAT	49	3571
877429	N/A	N/A	101479	101498	ATATAATTATGAAATCTATT	95	3572
877453	N/A	N/A	104214	104233	GAGTATGGATTGTCATGTCT	63	3573
877477	N/A	N/A	105993	106012	ACAAAAAGTCTTTTTGAGGC	48	3574
877501	N/A	N/A	108768	108787	TTACTACTATATATATATCA	72	3575
877525	N/A	N/A	111286	111305	CATGTCAGTTGGTTAGAACT	62	3576
877549	N/A	N/A	113456	113475	TATTACTACTTGCTATGAGG	55	3577
877573	N/A	N/A	116029	116048	ATGAGCTCTCTAGGCAGACA	40	3578
877597	N/A	N/A	118217	118236	AGTCTAATATTACACAGCAA	41	3579

[0667]

877621	N/A	N/A	120065	120084	TTTTTCCAGGTGGAAATATA	120	3580
877645	N/A	N/A	122402	122421	ATTCAAAAACTATTTAAATG	118	3581
877669	N/A	N/A	125328	125347	TAATGAGTACACAGTAATTC	54	3582
877693	N/A	N/A	128602	128621	TCAGATAATATGGTGGACAA	53	3583
877717	N/A	N/A	132890	132909	AGAGGCCCTACAAAGATTCA	92	3584
877741	N/A	N/A	136288	136307	TCAACAATATAGAGAGGATC	113	3585
877765	N/A	N/A	140272	140291	TGTATTTAATAGAAAATAGT	114	3586
877789	N/A	N/A	141697	141716	TGAAGTGCAAAGATAATTCT	129	3587
877813	N/A	N/A	144037	144056	CTGAGACAACCTATTGAGAG	67	3588
877837	N/A	N/A	145342	145361	CATATCACTTGTAATTTTGA	43	3589

표 48

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	18	222
876031	736	755	18635	18654	ACGCACTTAACAATATCATA	22	3590
876055	867	886	21698	21717	TTCCACCACAATATTATAAC	42	3591
876079	1298	1317	N/A	N/A	CTATGAGCTGGGAAATGGCC	62	3592
876103	1485	1504	35432	35451	ACTTTCAGCCACTTCAGGAG	38	3593
876127	1723	1742	41956	41975	CATTCTTGAAACACTGTTTT	39	3594
876151	2456	2475	62077	62096	TGGCTGTCACCTTTCCCAAT	33	3595
876175	3153	3172	73689	73708	CTCCAGCTTTTCAAGATGCT	33	3596
876199	3529	3548	77278	77297	ATGAAATGTGGTTCTTACTA	35	3597
876223	3854	3873	82199	82218	TGCAGTTTCTCTACTCTAGA	23	3598
876247	4317	4336	87221	87240	ATGAGTACTATAGAATTCCT	48	3599
876271	4753	4772	92176	92195	TCCGGTCAATTACGGGAAAT	36	3600
876295	5074	5093	98222	98241	TCTGGAATTTTTCTAGGAGC	26	150
876319	5454	5473	100443	100462	AATGTGGTCCACAACTTGGC	49	3601
876343	5792	5811	106483	106502	GCTGCTCGGTAAACTGATCC	46	3602
876367	6601	6620	129746	129765	TGCTTGCATTCCTGCTGTTG	43	3603
876391	7218	7237	141579	141598	AACAGGGCTATTTTGCTTAG	54	3604
876415	8131	8150	146300	146319	TACATTACATGGGAAACTGT	43	3605
876439	9021	9040	147190	147209	AATACAGAAAATCTTTCATC	120	3606
876463	N/A	N/A	4967	4986	ATCAGGCACTTCTGAACACC	51	3607
876487	N/A	N/A	7241	7260	AGTGAGTATTAAAATGTCAG	47	3608
876511	N/A	N/A	9214	9233	TGCTCCCCAAGTAATGAAGC	65	3609
876535	N/A	N/A	12417	12436	GATTTTAATCCCTATGTTAT	115	3610
876559	N/A	N/A	15046	15065	ACTTCAATATATTCCAGTGT	54	3611
876583	N/A	N/A	17338	17357	TGCTATTCTGACTTTTGACA	87	3612
876607	N/A	N/A	19605	19624	GTTAATGGTCACTTACAAAA	32	3613
876631	N/A	N/A	21986	22005	GACACTCCTTTTAAAAGTCC	33	3614

[0668]

876655	N/A	N/A	25054	25073	TTCAGCAACCACTCTCACTT	60	3615
876679	N/A	N/A	27604	27623	TTCATTGTGTAAAATAACTT	95	3616
876703	N/A	N/A	29976	29995	ATCACAGATGGCTCTGCAAT	56	3617
876727	N/A	N/A	32024	32043	ATAATAGACAATTTTACCAG	33	3618
876751	N/A	N/A	33545	33564	AGAACATTTTACACACTATC	52	3619
876775	N/A	N/A	35950	35969	CTATATAATCTTAGCATCTC	86	3620
876799	N/A	N/A	38144	38163	CATTGAGGTAAATGAGTACA	83	3621
876823	N/A	N/A	39741	39760	TTGATACCTAGAATGATACG	71	3622
876847	N/A	N/A	42026	42045	ATAGTATAAATACAGAAAAC	84	3623
876871	N/A	N/A	45585	45604	TTGGCTAACTGGAACCAGTT	63	3624
876895	N/A	N/A	47882	47901	GGAAGGAAAAAACGAATACC	61	3625
876919	N/A	N/A	49713	49732	ATCTTGAAATAGTAATGTAT	67	3626
876943	N/A	N/A	52094	52113	TGGGACTTGAATATAAATGT	97	3627
876967	N/A	N/A	54851	54870	TTGATAAGCAAAGTAGCCTT	34	3628
876991	N/A	N/A	57309	57328	TAAACTATTGGCAAACATAG	79	3629
877015	N/A	N/A	60005	60024	AGGTGATTTATGTTTTACTC	56	3630
877039	N/A	N/A	62783	62802	TCAGAAGATGGTAACTTACC	85	3631
877063	N/A	N/A	65433	65452	TAAGAGATACACCAGCAACT	91	3632
877087	N/A	N/A	67067	67086	GGTTTCTTAAGTGGGATACA	45	3633
877111	N/A	N/A	70265	70284	TACATAAGAAGAAATTTAAA	105	3634
877135	N/A	N/A	72531	72550	ATTAACACAAAACAACCCTC	63	3635
877159	N/A	N/A	73941	73960	CAGATCTGTTTCCATTGCCT	23	3636
877183	N/A	N/A	75798	75817	AGCAAACCCCTACTTACACA	37	3637
877207	N/A	N/A	78361	78380	TCTACAACTTTTAATAAAAG	85	3638
877231	N/A	N/A	81545	81564	AAAGATAAATTTACACATAT	76	3639
877238	N/A	N/A	82750	82769	AGAATTTTTATCCTTATACT	77	3640
877262	N/A	N/A	85277	85296	CCACTATTTGAAAAAATGTC	41	3641
877286	N/A	N/A	88222	88241	ATTCACTCCTAAATAAAATA	95	3642
877310	N/A	N/A	90580	90599	ATGATCTCTAATAGATTAAA	76	3643
877334	N/A	N/A	92439	92458	ACATGATTTGTCATGAACAC	19	3644
877358	N/A	N/A	94604	94623	TAAGTGCTCTGGGTCACACT	53	3645
877382	N/A	N/A	96108	96127	AGCACCAATACTCCAAAAAC	67	3646
877406	N/A	N/A	98871	98890	ATTAGTTATGCATAGACAAA	83	3647
877430	N/A	N/A	101490	101509	AATCTATGACAATATAATTA	102	3648
877454	N/A	N/A	104219	104238	ATATGGAGTATGGATTGTCA	46	3649
877478	N/A	N/A	106035	106054	ACTAGTTTTTATTCTACCTT	90	3650
877502	N/A	N/A	108861	108880	CTAACATATACTCTTGGAGC	44	3651
877526	N/A	N/A	111304	111323	AATCTTTTTTTTAATGCCCA	61	3652
877550	N/A	N/A	113493	113512	TGATGGGTTCTAGAGCAGAA	38	3653
877574	N/A	N/A	116095	116114	GCTAACACTTCATGACACAC	49	3654
877598	N/A	N/A	118289	118308	AGCATCAAAAATTCTGTGCT	51	3655
877622	N/A	N/A	120141	120160	GTGGTCCAGTCCACCTTCAT	61	3656
877646	N/A	N/A	122515	122534	TTATGCTTCCCTTCTTAGAA	63	3657
877670	N/A	N/A	125342	125361	AAAACATTCCAGGATAATGA	52	3658
877694	N/A	N/A	128625	128644	TAAAACATGACAAGAGTTCT	124	3659
877718	N/A	N/A	133009	133028	TCTTAATTTGGTAGTTAGAT	28	3660
877742	N/A	N/A	136525	136544	GATGAAAGTAGGCCCCACTC	70	3661
877766	N/A	N/A	140319	140338	TGTCAGAGAGCCACTACGCT	57	3662

[0669]

877790	N/A	N/A	141746	141765	TTCTCTATTCAGAGGCAGAA	61	3663
877814	N/A	N/A	144077	144096	TTCAACTAGAGAATGCAACA	58	3664
877838	N/A	N/A	145702	145721	AAAGATCCATCATAAAACAT	111	3665

표 49

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	28	222
876027	730	749	18629	18648	TTAACAATATCATATAATCT	6	3666
876051	838	857	21669	21688	TGCCACTCATGAGGACTTCC	39	3667
876075	1237	1256	29588	29607	TAAGGAGATTATTTAGTGCC	61	3668
876099	1481	1500	35428	35447	TCAGCCACTTCAGGAGAATG	53	3669
876123	1700	1719	41933	41952	ACCATATTTAGCTTATGATG	25	3670
876147	2450	2469	62071	62090	TCACCTTTCCCAATGCTTAT	77	3671
876171	2936	2955	72960	72979	AAATCTTCATGATCAAAAAT	85	3672
876195	3338	3357	76472	76491	GTAGGATCTAAAACCACTGA	22	3673
876219	3840	3859	82185	82204	TCTAGACCATAAATATGCTT	29	3674
876243	4312	4331	87216	87235	TACTATAGAATTCCTCACGA	58	3675
876267	4735	4754	92158	92177	ATTCAATTGGCACATTTTTA	49	3676
876291	5069	5088	98217	98236	AATTTTTCTAGGAGCTTAAA	107	3677
876315	5448	5467	100437	100456	GTCCACAACTTGGCCCAAAA	30	3678
876339	5694	5713	101332	101351	CAGGTCAGCCAAAATCAAGT	37	3679
876363	6466	6485	126582	126601	TTTCTTGAGGATTTTCTTTC	75	3680
876387	7046	7065	137450	137469	ATTACATTTCTTTCCGTTGA	53	3681
876411	7998	8017	146167	146186	AAATTATCGGCCTTATAAAT	96	3682
876435	8867	8886	147036	147055	GGCCAAAGAATTTACCGAAA	48	3683
876459	N/A	N/A	4386	4405	TTTTTAAGGCCCCCTTTAAA	95	3684
876483	N/A	N/A	7028	7047	TTAGGTCTGTCACAAGCTCT	50	3685
876507	N/A	N/A	8960	8979	CAGTCTGTTTACAAGATGCC	36	3686
876531	N/A	N/A	11871	11890	TGAACAGTTGGTTTGTACAG	67	3687
876555	N/A	N/A	14783	14802	GGACTGATGAGGACAATTCA	88	3688
876579	N/A	N/A	16929	16948	AGGTGATCTATCCCATTCTG	67	3689
876603	N/A	N/A	19458	19477	GTGGCTAAATTTCAAAGCCT	70	3690
876627	N/A	N/A	21316	21335	TGGAAATGTAATGTATTGGT	56	3691
876651	N/A	N/A	24654	24673	GCAGTTGGTTTAGACTCCCC	44	3692
876675	N/A	N/A	27306	27325	AGGAAAAACTTTACCTGATA	83	3693
876699	N/A	N/A	29666	29685	ATTTTCTATCATATAAAATC	93	3694
876723	N/A	N/A	31361	31380	TAAAATTTTGTATATGTCAT	146	3695
876747	N/A	N/A	33424	33443	AGGTCTTACTCAATAGTCAC	34	3696
876771	N/A	N/A	35347	35366	CTGAAATTAACTGAGATTTT	84	3697

[0670]

876795	N/A	N/A	37878	37897	TATAAAAATTAATCTAAGTG	85	3698
876819	N/A	N/A	39165	39184	CTGATTGAATAGCCACCAGA	110	3699
876843	N/A	N/A	41526	41545	AAGCTCAGAGTTACTTGGAC	52	3700
876867	N/A	N/A	45354	45373	GACGCGGCAACTGTGGCAAT	34	3701
876891	N/A	N/A	47370	47389	ATGAATGATTACCATGTAAG	87	3702
876915	N/A	N/A	49237	49256	TCCAACATCATATGACTGAT	62	3703
876939	N/A	N/A	51525	51544	CAGTTTCTCACCCTGTGTCC	50	3704
876963	N/A	N/A	54026	54045	AGTTACAAAAAATATTTCCT	79	3705
876987	N/A	N/A	56923	56942	GAATTATATTTTGAAGGGAG	66	3706
877011	N/A	N/A	59932	59951	CCATTTTATATTCTCTATTA	85	3707
877035	N/A	N/A	62618	62637	TACATGTAAGCATATAAAAA	116	3708
877059	N/A	N/A	64920	64939	CCTGATGGAATTTCAAAGTT	89	3709
877083	N/A	N/A	67061	67080	TTAAGTGGGATACAAAAAGC	65	3710
877107	N/A	N/A	69892	69911	ATATTTCTCTATCAAATACA	79	3711
877131	N/A	N/A	72432	72451	GGCTCCCAATTTCCTCAACT	25	3712
877155	N/A	N/A	73935	73954	TGTTTCCATTGCCTGCCCTC	62	3713
877179	N/A	N/A	75295	75314	AATTGAAGGATTACCAAGTT	67	3714
877203	N/A	N/A	78122	78141	TGCATGTTTAGTTTAAGACT	65	3715
877227	N/A	N/A	81187	81206	GTTTTTACACAATGATCCAC	57	3716
877234	N/A	N/A	82324	82343	TCATGAAATTGGTATTTAGA	73	3717
877258	N/A	N/A	84886	84905	AGAGATTTTAGGCAGAAGAG	68	3718
877282	N/A	N/A	87961	87980	TGTATGCAGCCAATTACATG	81	3719
877306	N/A	N/A	90436	90455	AAACCATTATGCCAGAATGC	54	3720
877330	N/A	N/A	91673	91692	CTTTTGGATATTATTATATT	76	3721
877354	N/A	N/A	94268	94287	AATAATTTTAGGAACTCGGG	85	3722
877378	N/A	N/A	95893	95912	ACATTATCTTGACTTTATCA	41	3723
877402	N/A	N/A	98345	98364	TAGACTACAGTTAGTTTGAC	49	3724
877426	N/A	N/A	101401	101420	ATTACCTAGGAGAAACTCTG	66	3725
877450	N/A	N/A	103499	103518	TTCTGTAAATGAACATGGGA	62	3726
877474	N/A	N/A	105725	105744	CTCTCCTGTTCAGAAACAAA	114	3727
877498	N/A	N/A	108194	108213	GAGGGCGAGGAAACTAACTC	66	3728
877522	N/A	N/A	111004	111023	CACCATTCCCTTAGTTTGCC	38	3729
877546	N/A	N/A	112841	112860	AAGTGCATGAGTCCACATAT	81	3730
877570	N/A	N/A	115680	115699	TAGAGTCAAGGACCTGGTGG	62	3731
877594	N/A	N/A	117784	117803	CTTCTGTTTGAGTATATAAT	83	3732
877618	N/A	N/A	119917	119936	TTAGAGTTGCATATGGTTTA	41	3733
877642	N/A	N/A	122346	122365	ATTTGGAATCACAGGCTCTT	66	3734
877666	N/A	N/A	125137	125156	TTATGCACTAAACAAAAAAA	106	3735
877690	N/A	N/A	128267	128286	TGGGACCCCAAAGGACTGCA	54	3736
877714	N/A	N/A	132254	132273	TTTATTTAATTTTCAGCAAT	78	3737
877738	N/A	N/A	135518	135537	ATATCAAAGGGATTCCTATA	113	3738
877762	N/A	N/A	139971	139990	CCTCTCAGTCGGTGTGTACT	102	3739
877786	N/A	N/A	141372	141391	TAGACTATTGCAATTATTTC	87	3740
877810	N/A	N/A	143858	143877	TATTTTCTTCACCATGTTCA	97	3741
877834	N/A	N/A	145268	145287	TACCATATGTAATATTTTCT	57	3742

[0671]

표 50

혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머를 가진 인간 LRRK2 RNA 의 퍼센트 대조군

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 (5'에서 3')	LRRK2 % 대조군	서열 번호
780241	3714	3733	82059	82078	GCTCATATCTAAAGACCGCA	24	222
803629	N/A	N/A	81591	81610	AAGCCATAGTGTTTGAAGGA	34	1791
876014	340	359	87848	87867	CCTGCTGCACACTCGCGACT	48	3743
876038	823	842	3731	3750	CTTCCACATTATTGCAAGGA	41	3744
876062	1022	1041	27997	28016	GCTGCATTCTCTGGGTACTG	28	3745
876086	1465	1484	35412	35431	AATGTATATGCTTCTGCATT	77	3746
876110	1494	1513	35441	35460	TTTACAGCCACTTTCAGCCA	63	3747
876134	2047	2066	N/A	N/A	ATCCTTTAGTCTGTATTTCA	83	3748
876158	2711	2730	65549	65568	GACAGCACATCTTCAGAAAA	64	3749
876182	3221	3240	76355	76374	AAATGTGTCAAACTCTTCAG	52	3750
876206	3747	3766	82092	82111	TGCGGGACCTGGTAGGTACT	57	3751
876230	3968	3987	83963	83982	CCCATTTCATTGGGAAAGGA	45	3752
876254	4520	4539	88621	88640	AGTTCCTTGGTGATTTTACT	45	3753
876278	4919	4938	93380	93399	ATTTTACAAAGCCACTTGGG	74	3754
876302	5195	5214	99201	99220	GGCATTTCATATAGTCGGAT	26	3755
876326	5644	5663	101282	101301	GCCTTGGTTGATCTGGATTT	32	3756
876350	6028	6047	113225	113244	GTGCAATCCTGTGCTGTAGG	42	3757
876374	6694	6713	N/A	N/A	TACTATCAGCAACTTCCTCA	100	3758
876398	7439	7458	143087	143106	CGTATAAGTCGACGAGTTGA	98	3759
876422	8442	8461	146611	146630	TCAGGGTATCCACATTCAAA	69	3760
876446	N/A	N/A	3734	3753	TTACCTGCTGCACACTCGCG	63	3761
876470	N/A	N/A	5242	5261	TCCTTATTTTCCAGCATACT	57	3762
876494	N/A	N/A	7823	7842	TCTCTCTAAGAGAGAAGGTT	64	3763
876518	N/A	N/A	10777	10796	CTTCATGGTTTGAATTCAAA	38	3764
876542	N/A	N/A	13175	13194	AAATCATCAATTGTATACCT	70	3765
876566	N/A	N/A	15815	15834	CTCAATCAGTACTTCTAGCC	79	3766
876590	N/A	N/A	17963	17982	AGTTTATCTAGCTTGAGAAT	67	3767
876614	N/A	N/A	20012	20031	AAACCATGGCCTTTCTCTAT	65	3768
876638	N/A	N/A	22763	22782	CCAAAACATTATTATCCAGA	58	3769
876662	N/A	N/A	26068	26087	AGAAATTTGGGTTCTCAGCC	64	3770
876686	N/A	N/A	28077	28096	AAATGCCTCTGTAAGAATCC	81	3771
876710	N/A	N/A	30722	30741	AAGTGAGGAGAAGAGAATGG	96	3772
876734	N/A	N/A	32675	32694	TCTAAAGGTGCCCCAACAGA	71	3773
876758	N/A	N/A	34015	34034	ATCACATACACATTCTAAAA	68	3774
876782	N/A	N/A	36424	36443	ATAGATTAGTTAGACTGATG	48	3775
876806	N/A	N/A	38547	38566	TTCTGCTTGAAATGTCTTCC	78	3776
876830	N/A	N/A	40757	40776	TCTTTGTTCTATCACTTGAG	72	3777
876854	N/A	N/A	42910	42929	CCTTCTTCTCTTTTTCATAC	42	3778
876878	N/A	N/A	46658	46677	TAAAAATTTAGTCCTTCATC	115	3779

[0672]

876902	N/A	N/A	48098	48117	AGGGTGCATAGTCTGTAGGT	52	3780
876926	N/A	N/A	50310	50329	CTGTTTGGCAGGCAAGGCCA	114	3781
876950	N/A	N/A	52848	52867	ATTCTAAATCCTGAATTCAA	102	3782
876974	N/A	N/A	55881	55900	AGGATGTTCATTTAACTATA	53	3783
876998	N/A	N/A	57829	57848	GAATATGGAAAGAGGAATAA	94	3784
877022	N/A	N/A	61188	61207	TCCATCAGTTACTGTGCTAA	58	3785
877046	N/A	N/A	63238	63257	GAAGAGAGAATTTAGAGCTA	81	3786
877070	N/A	N/A	66210	66229	AAAGCCCCTCACTCCATTTT	60	3787
877094	N/A	N/A	67516	67535	AAGTTAGTTGATTAAAAATT	120	3788
877118	N/A	N/A	71000	71019	ATAAATTTGGCTGGCAATAA	76	3789
877142	N/A	N/A	72845	72864	GTTAATGGTATTTATAATTA	86	3790
877166	N/A	N/A	74324	74343	ATTTTCAGAGAGCTATCCTA	103	3791
877190	N/A	N/A	76592	76611	CTTTCTTACCCTTCTAAAAT	71	3792
877214	N/A	N/A	79053	79072	CTGAGATGACACACTGACCA	50	3793
877245	N/A	N/A	83601	83620	CTCTTCAAGACATTGAAAGT	81	3794
877269	N/A	N/A	86919	86938	GAAATGAAGGGCTTTGGAAT	76	3795
877293	N/A	N/A	89053	89072	ATAAGAAGTTGAATCAGAAA	99	3796
877317	N/A	N/A	91034	91053	CTCTTAACCCAGAGAATTAG	82	3797
877341	N/A	N/A	93061	93080	ACAGAGCATATTTCACACAT	42	3798
877365	N/A	N/A	95209	95228	CCACAGAATCTTCAGGAATT	45	3799
877389	N/A	N/A	96646	96665	TTGGATAAATTATTCAACCT	70	3800
877413	N/A	N/A	99821	99840	TGATCATGCTAAACGCAAAA	90	3801
877437	N/A	N/A	102050	102069	GAATATTGAAACATGGTTAC	48	3802
877461	N/A	N/A	104931	104950	TCTTGGTATTCTCTCATTCT	46	3803
877485	N/A	N/A	106787	106806	TTACAACACACTATGTATCA	86	3804
877509	N/A	N/A	109992	110011	ATTAAACCAATATACCAAGG	60	3805
877533	N/A	N/A	111782	111801	GCAATTCAAAAAAAGTCCGA	58	3806
877557	N/A	N/A	114063	114082	TGAGAGAAATTGTTAGAAGC	85	3807
877581	N/A	N/A	116850	116869	TTTATAGAACACAGACTCTT	88	3808
877605	N/A	N/A	119162	119181	AGGGAGGTAAGATTCCACAG	62	3809
877629	N/A	N/A	121067	121086	CATATGTCAGAGGGTCCTAA	63	3810
877653	N/A	N/A	123315	123334	TTTGCTAAAATTATCTGTGC	65	3811
877677	N/A	N/A	126752	126771	GATGGTGAAAATTATAGGAG	50	3812
877701	N/A	N/A	129290	129309	AAAAACCCTTGGGCCAACAA	71	3813
877725	N/A	N/A	133380	133399	CCCTGCTGTGATAGGCTTGA	51	3814
877749	N/A	N/A	138071	138090	TTGAAAGAGGTTTATATTAA	95	3815
877773	N/A	N/A	140699	140718	GGTGTCACTGTCATATTATA	60	3816
877797	N/A	N/A	142490	142509	ATAGTCTAATTCATGACAAA	102	3817
877821	N/A	N/A	144612	144631	CTATGTAGGCCCTAGGCTAG	73	3818

[0673]

[0674] **실시예 5: 인간 LRRK2 RNA 발현 *시험관내*, 다중 용량에서 포스포로티오에이트 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머의 효과**

[0675] 상기 실시예 1로부터 선택된 변형된 올리고뉴클레오타이드는 SH-SY5Y 세포내 다양한 용량에서 시험되었다. 세포는, 아래 표에서 특정된 바와 같이, 20,000 세포/웰의 밀도로 플레이팅되었고 1.125 μM, 2.250 μM, 4.500 μM, 9.000 μM, 및 18.000 μM 농도의 변형된 올리고뉴클레오타이드로 전기천공을 사용하여 형질감염되었다. 대략 24 시간의 처리 기간 후, 총 RNA는 세포로부터 단리되었고 LRRK2 RNA 수준은 정량적 실시간 PCR에 의해 측정되었다. (실시예 1에서 본 명세서에 기재된) 인간 LRRK2 프라이머 프로브 세트 RTS3133_MGB는 RNA 수준을 측정하는데 사용되었다. LRRK2 RNA 수준은, RIBOGREEN®에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다. 결과는 미처리된 대조군 세포에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다. 아래 표에서 설명된 바와 같이, LRRK2 RNA 수준은 변형된 올리고뉴클레오타이드-처리된 세포에서 용량-의존적 방식으로 감소되었다. IC50은 Prism6 소프트웨어를 사용하는 "log(억제제) 대 반응 - 가변 경사 (4 파라미터)" 식을 사용하여 계산되었다.

표 51

SH-SY5Y 세포에서 인간 LRRK2 RNA 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)					IC_{50} (μM)
	1.125 μM	2.250 μM	4.500 μM	9.000 μM	18.000 μM	
438387	81	43	30	18	14	2
438429	119	109	116	89	81	31
438432	110	78	64	42	15	7
438543	94	85	69	44	42	10
438565	92	80	80	66	53	22
438569	94	79	65	51	47	12
438586	98	85	52	38	27	6
438587	91	80	58	43	32	7
438595	86	66	41	35	25	4
438597	45	39	37	32	18	n/a*
438602	59	73	50	30	33	4
438622	109	115	100	92	85	40
438625	110	108	96	94	81	36
422428	75	57	35	27	20	3
422433	75	56	32	18	15	3
422450	81	97	87	71	66	51
422451	74	52	40	29	26	3
422461	89	65	44	30	25	4
438538	72	54	33	20	16	3
438544	65	39	28	18	12	2
438545	90	60	37	15	13	3
438548	89	65	38	20	16	4
438550	95	78	59	34	15	6
438560	56	41	30	22	23	1
438588	65	57	49	26	17	3
438652	109	94	74	54	53	15

*IC_{50} 값은 계산될 수 없었다

[0676]

[0677] **실시예 6: 인간 LRRK2 RNA 발현 *시험관내*, 다중 용량에서 혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머의 효과**

[0678] 상기 실시예 2 및 3으로부터 선택된 변형된 올리고뉴클레오타이드는 SH-SY5Y 세포내 다양한 용량에서 시험되었다. 세포는, 아래 표에서 특정된 바와 같이, 20,000 세포/웰의 밀도로 플레이팅되었고 0.333 μM, 1.000 μM, 3.000 μM, 및 9.000 μM 농도의 변형된 올리고뉴클레오타이드로 전기천공을 사용하여 형질감염되었다. 대략 24 시간의 처리 기간 후, 총 RNA는 세포로부터 단리되었고 LRRK2 RNA 수준은 정량적 실시간 PCR에 의해 측정되었다. (실시예 2에서 상기 기재된) 인간 LRRK2 프라이머 프로브 세트 RTS3132는 RNA 수준을 측정하는데 사용되었다. LRRK2 RNA 수준은, RIBOGREEN®에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다. 결과는 미처리된 대조군 세포에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다. 아래 표에서 설명된 바와 같이, LRRK2 RNA 수준은 변형된 올리고뉴클레오타이드-처리된 세포에서 용량-의존적 방식으로 감소되었다. IC50은 Prism6 소프트웨어를 사용하는 "log(억제제) 대 반응 - 가변 경사 (4 파라미터)" 식을 사용하여 계산되었다.

표 52

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.333 μM	1.000 μM	3.000 μM	9.000 μM	
693423	62	46	45	13	0.9
693428	58	45	34	13	0.7
693430	68	28	32	26	0.6
725607	66	42	30	21	0.8
725608	54	44	36	40	0.4
780148	80	67	51	19	2.2
780162	56	35	29	19	0.4
780164	43	24	21	24	0.07
780166	60	51	26	18	0.8
780189	60	37	22	31	0.5
780202	70	42	36	20	0.9
780205	68	44	32	25	0.9
780210	62	56	31	25	1.0
780219	75	52	24	31	1.2
780236	42	34	29	19	0.1
780241	67	47	18	5	0.8
780243	37	41	26	25	n/a*
780254	68	37	35	19	0.8
780284	66	44	26	19	0.8

*IC_{50} 값은 계산될 수 없다

[0679]

표 53

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.333 μM	1.000 μM	3.000 μM	9.000 μM	
780254	61	45	23	17	0.7
780321	66	59	46	25	1.6
780347	55	47	43	47	0.8
780430	82	70	55	33	3.5
780442	80	81	43	31	3.0
780455	92	61	47	21	2.2
780461	74	90	72	40	7.3
780499	74	67	36	36	2.2
780535	86	71	75	63	>60
780549	56	31	19	2	0.4
780551	93	65	26	35	1.9
780602	52	41	27	17	0.4
780624	71	52	37	27	1.3
780649	67	40	29	12	0.7
780670	85	71	55	31	3.4
780685	73	43	29	15	0.9
780700	96	61	36	24	2.0
780704	84	86	45	37	3.8
780706	94	72	66	42	6.1

[0680]

[0681] **실시예 7: 인간 LRRK2 RNA 발현 *시험관내*, 다중 용량에서 혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머의 효과**

[0682] 상기 실시예 4로부터 선택된 변형된 올리고뉴클레오타이드는 SH-SY5Y 세포내 다양한 용량에서 시험되었다. 세포는, 아래 표에서 특정된 바와 같이, 20,000 세포/웰의 밀도로 플레이팅되었고 0.296, 0.888, 2.666, 및 8.000 μM 농도의 변형된 올리고뉴클레오타이드로 전기천공을 사용하여 형질감염되었다. 대략 24 시간의 처리 기간 후, 총 RNA는 세포로부터 단리되었고 LRRK2 RNA 수준은 정량적 실시간 PCR에 의해 측정되었다. (실시예 2에서

본 명세서에 기재된) 인간 LRRK2 프라이머 프로브 세트 RTS3132는 RNA 수준을 측정하는데 사용되었다. LRRK2 RNA 수준은, RIBOGREEN®에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다. 결과는 미처리된 대조군 세포에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다. 아래 표에서 설명된 바와 같이, LRRK2 RNA 수준은 변형된 올리고뉴클레오타이드-처리된 세포에서 용량-의존적 방식으로 감소되었다. IC50은 Prism6 소프트웨어를 사용하는 "log(억제제) 대 반응 - 가변 경사 (4 파라미터)" 식을 사용하여 계산되었다.

표 54

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.296 μM	0.888 μM	2.666 μM	8.000 μM	
780254	58	36	30	15	0.5
802655	103	90	87	20	5.0
802678	51	68	25	5	0.7
802685	110	82	43	13	2.3
802686	147	115	70	29	4.8
802688	87	67	40	15	1.7
802689	85	69	52	6	2.0
802700	163	84	29	29	2.0
802731	155	89	43	40	3.7
802746	120	78	65	18	3.5
802748	116	82	36	12	2.1
802758	119	71	31	5	1.7
802769	87	81	39	38	2.9
802778	97	53	56	30	2.6
802780	92	53	34	22	1.4
802784	84	82	42	26	2.5
802832	116	62	94	31	6.0
802888	58	54	26	10	0.7
802915	80	50	28	10	1.0

표 55

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.296 μM	0.888 μM	2.666 μM	8.000 μM	
780254	76	56	26	12	1.0
802845	127	100	43	13	1.0
802911	77	44	27	11	0.8
802924	184	159	59	18	n/a*
802934	158	108	93	47	7.6
802949	113	69	33	신호 없음	1.7
802962	128	150	93	27	6.1
802966	171	130	17	31	n/a*
802974	120	71	36	13	1.9
803000	106	158	57	36	4.9

[0683]

803021	80	112	75	70	22.1
803045	87	68	54	32	3.0
803046	70	69	28	14	1.2
803054	104	114	116	45	n/a*
803064	60	80	62	26	3.1
803065	101	89	27	55	4.0
803075	94	56	53	10	1.8
803112	90	37	27	11	0.9
803122	74	63	26	27	1.3

*IC_{50} 값은 계산될 수 없다

표 56

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.296 μM	0.888 μM	2.666 μM	8.000 μM	
780254	57	43	30	10	0.5
803102	76	76	46	28	2.4
803123	103	110	60	30	4.2
803172	104	87	82	46	7.3
803177	138	98	72	41	5.9
803181	142	84	86	50	8.0
803272	105	94	68	47	6.6
803285	87	80	56	38	4.1
803359	102	81	105	69	n/a*
803386	81	65	28	24	1.4
803436	116	97	59	81	n/a*
803470	60	61	25	44	1.1
803503	71	50	61	50	8.4
803517	75	48	58	22	1.7
803519	80	59	43	52	3.9
803571	65	57	36	26	1.1
803595	66	62	34	25	1.2
803603	86	65	59	29	3.0
803604	50	32	52	22	0.2

*IC_{50} 값은 계산될 수 없다

[0684]

표 57

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.296 μM	0.888 μM	2.666 μM	8.000 μM	
780254	54	45	18	22	0.4
780620	120	87	77	37	5.7
780624	133	66	38	62	5.5
803541	110	86	40	16	2.3
803628	140	77	57	15	3.0
803629	78	31	40	15	0.8
803640	116	125	81	39	6.4
803645	123	117	59	33	4.5
803665	154	121	68	48	6.8
803680	87	71	39	27	2.1
803682	94	64	31	17	1.5
803686	79	69	54	21	2.3
803744	85	50	29	20	1.1
803745	91	75	55	24	2.9
803769	60	79	48	19	1.9
803770	43	38	25	5	0.2
803771	49	47	20	11	0.4
803773	73	54	28	28	1.1
803782	75	61	22	16	1.1

[0685]

[0686] **실시예 8: 인간 LRRK2 RNA 발현 *시험관내*, 다중 용량에서 혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머의 효과**

[0687] 상기 실시예 4로부터 선택된 변형된 올리고뉴클레오타이드는 SH-SY5Y 세포내 다양한 용량에서 시험되었다. 세포는, 아래 표에서 특정된 바와 같이, 20,000 세포/웰의 밀도로 플레이팅되었고 0.444, 1.333, 4.000, 및 12.000 μM 농도의 변형된 올리고뉴클레오타이드로 전기천공을 사용하여 형질감염되었다. 대략 24 시간의 처리 기간 후, 총 RNA는 세포로부터 단리되었고 LRRK2 RNA 수준은 정량적 실시간 PCR에 의해 측정되었다. (실시예 2에서 본 명세서에 기재된) 인간 LRRK2 프라이머 프로브 세트 RTS3132는 RNA 수준을 측정하는데 사용되었다. LRRK2 RNA 수준은, RIBOGREEN®에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다. 결과는 미처리된 대조군 세포에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다. 아래 표에서 설명된 바와 같이, LRRK2 RNA 수준은 변형된 올리고뉴클레오타이드-처리된 세포에서 용량-의존적 방식으로 감소되었다. IC50은 Prism6 소프트웨어를 사용하는 "log(억제제) 대 반응 - 가변 경사 (4 파라미터)" 식을 사용하여 계산되었다.

표 58

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	
780241	57	29	9	3	0.6
876032	80	56	25	12	1.6
876033	65	45	45	8	1.3
876035	65	59	35	17	1.6
876200	105	49	29	17	1.9
876201	83	84	45	22	3.8
876204	58	38	22	14	0.7
876224	74	48	41	15	1.6
876274	70	48	26	16	1.2
876298	60	47	42	28	1.2
876611	71	52	27	16	1.4
876683	79	58	23	27	1.8
876706	80	57	43	17	2.2
876850	89	64	37	16	2.4
876899	42	29	18	9	0.3
877113	53	44	34	10	0.7
877160	88	57	29	14	1.9
877239	115	93	59	31	6.1
877722	72	43	38	28	1.5

표 59

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	
780241	54	37	41	19	n/a*
803629	90	60	31	31	2.5
876062	62	38	16	7	0.8
876084	114	89	42	18	3.7
876109	84	58	59	40	5.6
876156	80	68	28	31	2.5
876180	79	53	41	15	1.9
876181	73	51	31	33	1.7
876276	93	51	19	11	1.5
876301	55	41	32	7	0.7
876302	47	25	21	7	0.3

[0688]

876326	66	50	35	12	1.3
876900	63	42	21	13	0.9
876901	63	56	36	29	1.6
877068	66	42	17	5	0.9
877292	53	34	16	28	0.4
877364	71	53	28	31	1.6
877388	57	56	34	37	1.3
877748	71	58	40	24	2.0

*IC_{50} 값은 계산될 수 없다

표 60

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	
780241	87	35	22	14	1.2
876038	68	39	40	32	1.3
876041	78	60	31	23	2.0
876042	52	34	25	12	0.5
876088	77	61	56	20	3.1
876089	80	76	48	15	3.2
876090	73	53	38	22	1.8
876185	55	52	32	15	0.9
876186	52	33	23	11	0.5
876282	53	35	25	11	0.5
876328	79	60	25	15	1.7
876401	83	60	52	42	5.1
876518	75	75	39	22	2.8
876713	61	59	50	19	1.9
876905	75	58	42	25	2.3
877098	82	54	34	24	2.0
877170	71	60	35	24	1.9
877392	68	48	31	23	1.3
877753	67	55	26	22	1.4

표 61

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	

[0689]

780241	70	44	39	18	1.4
876019	67	45	28	11	1.1
876020	67	55	49	25	2.2
876066	60	62	36	19	1.5
876139	78	37	39	10	1.3
876140	80	47	36	14	1.6
876255	72	39	33	27	1.2
876260	70	46	22	29	1.2
876261	33	25	18	4	n/a*
876283	75	60	29	13	1.7
876284	48	35	35	18	n/a*
876303	48	21	32	2	0.3
876499	66	72	42	26	2.7
876735	67	43	28	7	1.0
876927	63	42	37	41	1.2
877119	61	31	35	4	0.7
877246	78	58	43	34	2.9
877370	69	58	46	40	3.3
877635	77	82	46	24	3.7

*IC_{50} 값은 계산될 수 없다

표 62

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	
780241	62	42	16	23	0.8
780624	70	37	21	6	0.9
803640	80	34	53	43	3.0
876141	66	50	30	17	1.2
876143	70	55	38	29	1.9
876165	110	74	54	18	4.1
876166	64	53	34	27	1.4
876189	62	33	24	22	0.7
876190	44	27	34	10	0.2
876213	71	50	37	12	1.5
876237	52	41	20	15	0.6
876262	59	37	21	13	0.7
876263	61	36	36	23	0.8
876285	68	62	31	23	1.8
876286	69	67	33	21	2.0

[0690]

876645	94	59	47	17	2.8
876766	67	37	26	13	0.9
876790	58	41	33	13	0.8
877222	68	48	32	20	1.3

표 63

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	
780241	71	54	41	27	2.0
876072	73	57	40	29	2.2
876073	72	52	24	25	1.4
876095	101	80	61	31	5.8
876097	55	44	42	24	n/a*
876168	64	45	21	9	0.9
876215	88	62	37	13	2.3
876288	75	62	28	6	1.7
876289	73	65	41	20	2.3
876335	77	75	43	25	3.2
876527	90	73	41	21	3.1
876769	78	67	41	31	1.5
877176	75	55	41	7	1.8
877303	61	45	23	19	0.8
877328	64	38	27	12	0.9
877375	82	68	47	28	3.5
877615	58	61	33	21	1.4
877616	75	50	25	19	1.4
877806	83	76	50	26	4.0

*IC_{50} 값은 계산될 수 없다

표 64

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	
780241	66	53	29	24	1.4
876050	83	58	52	17	2.8
876052	72	48	53	17	2.0
876053	75	47	36	20	1.6

[0691]

876098	95	59	38	16	2.4
876149	71	52	28	20	1.4
876218	79	61	44	17	2.4
876220	68	43	39	18	1.3
876221	48	29	16	9	0.4
876293	72	54	21	17	1.3
876337	85	90	59	19	4.9
876362	86	73	54	26	4.2
876385	81	62	36	20	2.3
876604	48	27	23	16	0.3
876725	66	50	39	35	1.7
876890	76	57	37	21	2.0
877156	80	58	44	28	2.7
877355	71	46	42	14	1.5
877356	49	41	24	29	0.3

표 65

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	
780241	75	62	42	15	2.2
876027	87	76	74	54	n/a*
876030	75	60	44	18	2.3
876031	69	44	43	13	1.4
876123	68	48	28	27	1.3
876150	82	55	48	27	2.8
876195	77	51	31	45	2.4
876219	77	65	46	24	2.9
876222	102	68	54	21	3.9
876223	74	58	41	16	2.0
876294	44	25	16	10	0.3
876295	71	48	51	36	2.7
876315	75	58	46	41	3.7
877131	83	67	43	23	2.9
877159	68	59	41	24	2.0
877182	104	88	70	19	5.9
877334	93	87	51	22	4.4
877357	97	84	51	25	4.5
877718	73	57	51	32	3.0

[0692]

*IC_{50} 값은 계산될 수 없다

표 66
SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	
780241	63	36	24	23	0.8
803627	76	52	30	10	1.4
876008	59	56	33	31	1.3
876011	90	66	45	29	3.4
876034	102	67	39	28	3.2
876081	80	69	56	29	4.2
876106	64	43	31	23	1.0
876203	60	40	23	7	0.8
876225	77	54	41	32	2.4
876249	81	69	37	33	3.1
876321	74	63	43	21	2.4
876540	90	69	44	22	3.1
876704	83	73	49	47	6.8
876731	70	49	39	40	2.1
877088	77	61	38	31	2.6
877112	65	52	28	17	1.2
877161	91	61	62	19	3.8
877289	73	55	34	20	1.7
877337	71	57	31	22	1.7

표 67
SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	
780241	50	107	20	6	n/a*
876015	89	63	46	35	3.8
876039	64	52	30	29	1.3
876043	56	41	20	6	0.7
876091	90	59	30	20	2.1
876092	72	49	33	21	1.5
876093	58	97	31	27	3.1
876187	75	55	47	21	2.2

[0693]

876235	72	51	28	20	1.4
876380	86	57	41	27	2.6
876639	76	62	42	35	3.0
876668	75	54	31	22	1.7
876732	77	52	44	24	2.2
876741	75	113	46	51	9.0
876852	70	53	38	28	1.8
877171	57	39	32	26	0.7
877395	62	35	22	26	0.7
877396	77	42	32	7	1.2
877587	108	83	48	46	6.7

*IC_{50} 값은 계산될 수 없다

표 68

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	
780241	52	36	33	11	0.5
876119	80	67	42	22	2.8
876169	64	50	34	26	1.3
876239	71	44	29	23	1.2
876287	55	41	29	23	0.6
876334	64	51	44	37	2.0
876528	83	49	31	19	1.7
876649	78	60	37	32	2.5
876694	66	48	32	26	1.3
876912	68	48	25	30	1.2
876960	52	32	26	8	0.5
877102	67	48	30	32	1.3
877128	66	53	35	30	1.6
877198	73	52	35	17	1.6
877252	75	73	34	31	2.9
877326	50	40	33	12	0.5
877327	78	53	27	25	1.7
877349	47	41	33	24	0.3
877493	88	75	44	37	0.4

표 69

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물	LRRK2 발현 (% 대조군)	IC_{50}

[0694]

번호	0.444 μM	1.333 μM	4.000 μM	12.000 μM	(μM)
780241	63	34	25	9	0.8
803643	49	59	54	32	1.7
876049	72	49	46	20	1.8
876074	54	32	28	7	0.5
876100	91	50	32	17	1.9
876124	61	37	17	23	0.7
876146	52	36	30	26	0.4
876170	78	48	41	25	1.9
876173	65	51	23	30	1.2
876244	71	52	29	31	1.6
876482	84	83	48	23	4.0
876553	79	54	32	23	1.8
876748	75	45	25	14	1.2
876821	83	64	40	26	2.8
877204	101	76	45	29	4.1
877305	63	41	28	17	0.9
877307	72	50	31	25	1.5
877496	71	59	34	24	1.9
877617	62	71	31	20	1.8

표 70

SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)				IC_{50} (μM)
	0.444 μM	1.333 μM	4.000 μM	12.000 μM	
780241	62	39	34	7	0.9
876054	72	74	42	27	3.0
876151	66	62	53	34	3.5
876175	95	48	36	29	2.3
876197	75	64	37	29	2.5
876318	68	58	39	16	1.7
876339	91	77	43	25	3.6
876414	77	52	48	25	2.4
876507	103	80	66	46	9.2
876607	79	57	43	25	2.4
876631	68	43	25	25	1.1
876727	93	79	59	32	5.6
876747	75	54	35	19	1.8
876867	71	54	25	13	1.3

[0695]

877524	106	106	71	42	9.0
877573	75	59	36	28	2.1
877597	88	79	45	33	4.3
877644	94	67	41	45	4.8
877692	78	67	53	25	3.5

[0696]

[0697] **실시예 9: 인간 LRRK2 RNA에 상보성인 혼합된 인터뉴클레오사이드 연결기가 있는 갭머의 설계**

[0698] 인간 LRRK2 핵산에 상보성인 변형된 올리고뉴클레오타이드는 설계되었다. 표 71에서 변형된 올리고뉴클레오타이드는 갭머이다. 갭머는 2'-데옥시뉴클레오사이드를 포함하는 그리고 및 cEt 뉴클레오사이드 및/또는 2'-MOE 뉴클레오사이드를 포함하는 5' 말단 및 3' 말단 둘 모두에서 윙 단편에 의해 측접되는 중심 갭 단편을 가지고 있다. 각 갭머 전반에 걸쳐 모든 시토신 잔기는 5'-메틸 시토신이다. 인터뉴클레오사이드 연결기는 혼합된 포스포디에스테르 인터뉴클레오사이드 연결기 및 포스포로티오에이트 인터뉴클레오사이드 연결기이다. 서열 및 화학 표기법 칼럼은, 5'-메틸 시토신, 당 화학, 및 인터뉴클레오사이드 연결기 화학을 포함하는, 서열을 특정하고, 여기서 첨자 'd'는 2'-데옥시리보오스 당을 나타내고; 첨자 'e'는 2'-MOE 변형된 당을 나타내고; 첨자 'k'는

cEt 변형된 당을 나타내고; 첨자 'o'는 포스포디에스테르 인터뉴클레오사이드 연결기를 나타내고; 첨자 's'는 포스포로티오에이트 인터뉴클레오사이드 연결기를 나타내고; 시토신 잔기 앞에 'm' 첨자는 5-메틸 시토신을 나타낸다. "개시 부위"는 갭머가 인간 핵산 서열에서 상보성인 5'-최말단 뉴클레오사이드를 나타낸다. "중단 부위"는 갭머가 인간 핵산 서열에서 상보성인 3'-최말단 뉴클레오사이드를 나타낸다.

[0699] 아래 표에서 열거된 각 변형된 올리고뉴클레오타이드는, 명시된 바와 같이, 인간 LRRK2 핵산 서열 서열번호: 1 또는 서열번호: 2에 상보성이다. 'N/A'는 변형된 올리고뉴클레오타이드가 100% 상보성을 가진 그 특정 핵산 서열에 상보성이지 않다는 것을 나타낸다.

표 71

인간 LRRK2 RNA에 상보성인 변형된 올리고뉴클레오타이드

화합물 번호	서열 번호: 1 개시 부위	서열 번호: 1 중단 부위	서열 번호: 2 개시 부위	서열 번호: 2 중단 부위	서열 및 화학 표기법 (5'에서 3')	서열 번호
872246	3714	3733	82059	82078	$G_{es}{}^{m}C_{eo}T_{eo}{}^{m}C_{es}A_{es}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}{}^{m}C_{eo}{}^{m}C_{eo}G_{es}{}^{m}C_{es}A_{e}$	222
872247	N/A	N/A	52154	52173	$G_{es}{}^{m}C_{eo}{}^{m}C_{eo}A_{es}A_{es}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}T_{eo}G_{eo}{}^{m}C_{es}A_{es}G_{e}$	599
872248	3494	3513	77243	77262	$A_{es}G_{eo}T_{eo}T_{es}{}^{m}C_{es}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{eo}A_{eo}G_{es}G_{es}G_{e}$	217
872249	7776	7795	145945	145964	$G_{es}A_{eo}G_{eo}T_{es}A_{es}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{eo}T_{eo}G_{es}A_{es}A_{e}$	398
872250	988	1007	27963	27982	${}^{m}C_{es}{}^{m}C_{eo}A_{eo}{}^{m}C_{es}A_{es}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{eo}T_{eo}T_{es}{}^{m}C_{es}G_{e}$	293
872251	3714	3733	82059	82078	$G_{es}{}^{m}C_{eo}T_{es}{}^{m}C_{es}A_{es}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}{}^{m}C_{eo}{}^{m}C_{eo}G_{es}{}^{m}C_{es}A_{e}$	222
872252	N/A	N/A	52154	52173	$G_{es}{}^{m}C_{eo}{}^{m}C_{es}A_{es}A_{es}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}T_{eo}G_{eo}{}^{m}C_{es}A_{es}G_{e}$	599
872253	3494	3513	77243	77262	$A_{es}G_{eo}T_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{eo}A_{eo}G_{es}G_{es}G_{e}$	217
872254	7776	7795	145945	145964	$G_{es}A_{eo}G_{es}T_{es}A_{es}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{eo}T_{eo}G_{es}A_{es}A_{e}$	398
872255	988	1007	27963	27982	${}^{m}C_{es}{}^{m}C_{eo}A_{es}{}^{m}C_{es}A_{es}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{eo}T_{eo}T_{es}{}^{m}C_{es}G_{e}$	293
872256	3714	3733	82059	82078	$G_{es}{}^{m}C_{eo}T_{es}{}^{m}C_{es}A_{es}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}{}^{m}C_{es}{}^{m}C_{eo}G_{es}{}^{m}C_{es}A_{e}$	222
872257	N/A	N/A	52154	52173	$G_{es}{}^{m}C_{eo}{}^{m}C_{es}A_{es}A_{es}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}T_{es}G_{eo}{}^{m}C_{es}A_{es}G_{e}$	599
872258	3494	3513	77243	77262	$A_{es}G_{eo}T_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{es}A_{eo}G_{es}G_{es}G_{e}$	217
872259	7776	7795	145945	145964	$G_{es}A_{eo}G_{es}T_{es}A_{es}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{es}T_{eo}G_{es}A_{es}A_{e}$	398
872260	988	1007	27963	27982	${}^{m}C_{es}{}^{m}C_{eo}A_{es}{}^{m}C_{es}A_{es}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{es}T_{eo}T_{es}{}^{m}C_{es}G_{e}$	293
872261	3714	3733	82059	82078	$G_{es}{}^{m}C_{es}T_{es}{}^{m}C_{es}A_{es}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}{}^{m}C_{es}{}^{m}C_{eo}G_{es}{}^{m}C_{es}A_{e}$	222
872262	N/A	N/A	52154	52173	$G_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{es}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}T_{es}G_{eo}{}^{m}C_{es}A_{es}G_{e}$	599
872263	3494	3513	77243	77262	$A_{es}G_{es}T_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{es}A_{eo}G_{es}G_{es}G_{e}$	217
872264	7776	7795	145945	145964	$G_{es}A_{es}G_{es}T_{es}A_{es}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{es}T_{eo}G_{es}A_{es}A_{e}$	398
872265	988	1007	27963	27982	${}^{m}C_{es}{}^{m}C_{es}A_{es}{}^{m}C_{es}A_{es}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{es}T_{eo}T_{es}{}^{m}C_{es}G_{e}$	293
872266	3712	3731	82057	82076	$T_{es}{}^{m}C_{eo}A_{es}T_{es}A_{es}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}G_{es}{}^{m}C_{eo}A_{es}A_{es}G_{e}$	1129
872267	3713	3732	82058	82077	${}^{m}C_{es}T_{eo}{}^{m}C_{es}A_{es}T_{es}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{es}G_{eo}{}^{m}C_{es}A_{es}A_{e}$	1130
872268	3715	3734	82060	82079	$T_{es}G_{eo}{}^{m}C_{es}T_{es}{}^{m}C_{es}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{ds}$	1131

[0700]

					$G_{ds}A_{es}{}^{m}C_{eo}{}^{m}C_{es}G_{es}{}^{m}C_{e}$	
872269	3716	3735	82061	82080	$^{m}C_{es}T_{eo}G_{es}{}^{m}C_{es}T_{es}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{es}A_{eo}{}^{m}C_{es}{}^{m}C_{es}G_{e}$	1132
872270	3717	3736	82062	82081	$G_{es}{}^{m}C_{eo}T_{es}G_{es}{}^{m}C_{es}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{es}G_{eo}A_{es}{}^{m}C_{es}{}^{m}C_{e}$	1133
872271	N/A	N/A	52151	52170	$A_{es}A_{eo}A_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}T_{ds}G_{ds}{}^{m}C_{ds}A_{es}G_{eo}A_{es}A_{es}A_{e}$	1677
872272	N/A	N/A	52152	52171	$^{m}C_{es}A_{eo}A_{es}A_{es}{}^{m}C_{es}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}T_{ds}G_{ds}{}^{m}C_{es}A_{eo}G_{es}A_{es}A_{e}$	1678
872273	N/A	N/A	52153	52172	$^{m}C_{es}{}^{m}C_{eo}A_{es}A_{es}A_{es}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}T_{ds}G_{es}{}^{m}C_{eo}A_{es}G_{es}A_{e}$	1679
872274	N/A	N/A	52155	52174	$T_{es}G_{eo}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{es}T_{eo}G_{es}{}^{m}C_{es}A_{e}$	1680
872275	N/A	N/A	52156	52175	$T_{es}T_{eo}G_{es}{}^{m}C_{es}{}^{m}C_{es}A_{ds}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{es}A_{eo}T_{es}G_{es}{}^{m}C_{e}$	1681
872276	N/A	N/A	52157	52176	$T_{es}T_{eo}T_{es}G_{es}{}^{m}C_{es}{}^{m}C_{ds}A_{ds}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}A_{ds}A_{es}G_{eo}A_{es}T_{es}G_{e}$	1682
872277	3495	3514	77244	77263	$^{m}C_{es}A_{eo}G_{es}T_{es}T_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{es}A_{eo}A_{es}G_{es}G_{e}$	1107
872278	3496	3515	77245	77264	$T_{es}{}^{m}C_{eo}A_{es}G_{es}T_{es}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{es}{}^{m}C_{eo}A_{es}A_{es}G_{e}$	1108
872279	3497	3516	77246	77265	$T_{es}T_{eo}{}^{m}C_{es}A_{es}G_{es}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{es}T_{eo}{}^{m}C_{es}A_{es}A_{e}$	1109
872280	7773	7792	145942	145961	$T_{es}A_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}T_{ds}G_{ds}A_{es}A_{eo}{}^{m}C_{es}A_{es}T_{e}$	1432
872281	7774	7793	145943	145962	$G_{es}T_{eo}A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}T_{ds}G_{es}A_{eo}A_{es}{}^{m}C_{es}A_{e}$	1433
872282	7775	7794	145944	145963	$A_{es}G_{eo}T_{es}A_{es}{}^{m}C_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}T_{es}G_{eo}A_{es}A_{es}{}^{m}C_{e}$	1434
872283	7777	7796	145946	145965	$T_{es}G_{eo}A_{es}G_{es}T_{es}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{es}G_{eo}T_{es}G_{es}A_{e}$	1435
872284	7778	7797	145947	145966	$G_{es}T_{eo}G_{es}A_{es}G_{es}T_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{es}T_{eo}G_{es}T_{es}G_{e}$	1436
872285	7779	7798	145948	145967	$T_{es}G_{eo}T_{es}G_{es}A_{es}G_{ds}T_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{es}A_{eo}T_{es}G_{es}T_{e}$	1437
874144	N/A	N/A	82056	82075	$^{m}C_{es}A_{eo}T_{eo}A_{eo}T_{es}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}G_{ds}{}^{m}C_{eo}A_{eo}A_{es}G_{es}{}^{m}C_{e}$	3820
874145	3493	3512	77242	77261	$G_{es}T_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}A_{eo}G_{eo}G_{es}G_{es}G_{e}$	3821
874146	3492	3511	77241	77260	$T_{es}T_{eo}{}^{m}C_{eo}{}^{m}C_{eo}T_{es}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}A_{ds}G_{eo}G_{eo}G_{es}G_{es}G_{e}$	3822
874147	3491	3510	77240	77259	$T_{es}{}^{m}C_{eo}{}^{m}C_{eo}T_{eo}T_{es}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}A_{ds}G_{ds}G_{eo}G_{eo}G_{es}G_{es}A_{e}$	3823
874148	4117	4136	86612	86631	$T_{es}{}^{m}C_{eo}A_{eo}T_{eo}A_{es}A_{ds}G_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}G_{eo}G_{eo}T_{es}T_{es}A_{e}$	3824
874149	N/A	N/A	82056	82075	$^{m}C_{es}A_{eo}T_{es}A_{es}T_{es}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}G_{ds}{}^{m}C_{es}A_{eo}A_{es}G_{es}{}^{m}C_{e}$	3820
874150	3493	3512	77242	77261	$G_{es}T_{eo}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}A_{es}G_{eo}G_{es}G_{es}G_{e}$	3821
874151	3492	3511	77241	77260	$T_{es}T_{eo}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}A_{ds}G_{es}G_{eo}G_{es}G_{es}G_{e}$	3822
890206	N/A	N/A	61977	61996	$^{m}C_{es}T_{eo}T_{eo}T_{eo}{}^{m}C_{es}T_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}A_{eo}T_{eo}T_{es}A_{es}A_{e}$	3825

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890207	N/A	N/A	61978	61997	$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}T_{es}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{eo}A_{eo}T_{es}T_{es}A_{e}$	3826
890208	N/A	N/A	61979	61998	$^{m}C_{es}T_{eo}{}^{m}C_{eo}T_{eo}T_{es}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{eo}T_{eo}A_{es}T_{es}T_{e}$	3827
890209	N/A	N/A	61980	61999	$T_{es}{}^{m}C_{eo}T_{eo}{}^{m}C_{eo}T_{es}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}{}^{m}C_{eo}{}^{m}C_{eo}T_{es}A_{es}T_{e}$	3828
934514	879	898	21710	21729	$T_{es}G_{eo}{}^{m}C_{es}T_{es}T_{es}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{es}A_{eo}{}^{m}C_{es}{}^{m}C_{es}A_{e}$	862
934515	880	899	21711	21730	$A_{es}T_{eo}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{es}{}^{m}C_{eo}A_{es}{}^{m}C_{es}{}^{m}C_{e}$	863
934516	837	856	21668	21687	$G_{es}{}^{m}C_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{es}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{es}T_{eo}{}^{m}C_{es}{}^{m}C_{es}A_{e}$	2833
934517	840	859	21671	21690	$A_{es}T_{eo}T_{es}G_{es}{}^{m}C_{es}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}G_{ds}G_{es}A_{eo}{}^{m}C_{es}T_{es}T_{e}$	3362
934517	840	859	21671	21690	$A_{es}T_{eo}T_{es}G_{es}{}^{m}C_{es}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}G_{ds}G_{es}A_{eo}{}^{m}C_{es}T_{es}T_{e}$	3362
934518	846	865	21677	21696	$^{m}C_{es}{}^{m}C_{eo}T_{es}G_{es}A_{es}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}G_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{es}A_{eo}T_{es}G_{es}A_{e}$	3514
934518	846	865	21677	21696	$^{m}C_{es}{}^{m}C_{eo}T_{es}G_{es}A_{es}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}G_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{es}A_{eo}T_{es}G_{es}A_{e}$	3514
934519	N/A	N/A	23873	23892	$T_{es}G_{eo}{}^{m}C_{es}A_{es}T_{es}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{es}A_{eo}A_{es}{}^{m}C_{es}A_{e}$	2706
934520	1233	1252	29584	29603	$G_{es}A_{eo}G_{es}A_{es}T_{es}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}{}^{m}C_{es}{}^{m}C_{eo}A_{es}G_{es}{}^{m}C_{e}$	3287
934521	1426	1445	35373	35392	$G_{es}T_{eo}A_{es}T_{es}T_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}A_{ds}T_{ds}A_{ds}A_{es}{}^{m}C_{eo}A_{es}G_{es}T_{e}$	917
934522	1435	1454	35382	35401	$^{m}C_{es}A_{eo}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}G_{ds}T_{ds}G_{ds}T_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{es}T_{eo}T_{es}T_{es}T_{e}$	918
934523	1488	1507	35435	35454	$G_{es}{}^{m}C_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{es}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{es}T_{eo}{}^{m}C_{es}A_{es}G_{e}$	922
934524	1700	1719	41933	41952	$A_{es}{}^{m}C_{eo}{}^{m}C_{es}A_{es}T_{es}A_{ds}T_{ds}T_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}T_{es}G_{eo}A_{es}T_{es}G_{e}$	3670
934525	1701	1720	41934	41953	$A_{es}A_{eo}{}^{m}C_{es}{}^{m}C_{es}A_{es}T_{ds}A_{ds}T_{ds}T_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{es}T_{eo}G_{es}A_{es}T_{e}$	3365
934526	N/A	N/A	48094	48113	$T_{es}G_{eo}{}^{m}C_{es}A_{es}T_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}G_{ds}T_{ds}A_{ds}G_{ds}G_{ds}T_{es}A_{eo}G_{es}T_{es}A_{e}$	2260
934528	2267	2286	56275	56294	$^{m}C_{es}T_{eo}G_{es}T_{es}T_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}G_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{es}A_{eo}{}^{m}C_{es}G_{es}{}^{m}C_{e}$	2685
934529	2452	2471	62073	62092	$T_{es}G_{eo}T_{es}{}^{m}C_{es}A_{es}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{es}G_{eo}{}^{m}C_{es}T_{es}T_{e}$	3366
934530	2453	2472	62074	62093	$^{m}C_{es}T_{eo}G_{es}T_{es}{}^{m}C_{es}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{es}T_{eo}G_{es}{}^{m}C_{es}T_{e}$	3443
934531	2454	2473	62075	62094	$G_{es}{}^{m}C_{eo}T_{es}G_{es}T_{es}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{es}A_{eo}T_{es}G_{es}{}^{m}C_{e}$	3518
934532	2456	2475	62077	62096	$T_{es}G_{eo}G_{es}{}^{m}C_{es}T_{es}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{es}{}^{m}C_{eo}A_{es}A_{es}T_{e}$	3595
934533	2363	2382	61984	62003	$^{m}C_{es}T_{eo}G_{es}{}^{m}C_{es}T_{es}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{es}A_{eo}T_{es}A_{es}{}^{m}C_{e}$	258
934534	2871	2890	71714	71733	$^{m}C_{es}T_{eo}G_{es}T_{es}A_{es}A_{ds}T_{ds}A_{ds}{}^{m}C_{ds}G_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{es}{}^{m}C_{eo}G_{es}G_{es}T_{e}$	3140
934535	N/A	N/A	73941	73960	$^{m}C_{es}A_{eo}G_{es}A_{es}T_{es}{}^{m}C_{ds}T_{ds}G_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{es}G_{eo}{}^{m}C_{es}{}^{m}C_{es}T_{e}$	3636
934536	3582	3601	77331	77350	$G_{es}G_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{es}T_{ds}G_{ds}A_{ds}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{es}A_{eo}{}^{m}C_{es}T_{es}T_{e}$	219

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934537	3850	3869	82195	82214	$G_{es}T_{eo}T_{es}T_{es}{}^{m}C_{es}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}G_{ds}A_{es}{}^{m}C_{eo}{}^{m}C_{es}A_{es}T_{e}$	3369
934538	3852	3871	82197	82216	$^{m}C_{es}A_{eo}G_{es}T_{es}T_{es}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{es}G_{eo}A_{es}{}^{m}C_{es}{}^{m}C_{e}$	3446
934540	N/A	N/A	91040	91059	$A_{es}T_{eo}G_{es}T_{es}A_{es}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{es}A_{eo}G_{es}A_{es}G_{e}$	1828
934541	N/A	N/A	91041	91060	$^{m}C_{es}A_{eo}T_{es}G_{es}T_{es}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{es}{}^{m}C_{eo}A_{es}G_{es}A_{e}$	1829
934542	N/A	N/A	91046	91065	$G_{es}T_{eo}T_{es}T_{es}T_{es}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{es}T_{eo}A_{es}A_{es}{}^{m}C_{e}$	1833
934543	N/A	N/A	91047	91066	$T_{es}G_{eo}T_{es}T_{es}T_{es}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{es}T_{eo}T_{es}A_{es}A_{e}$	1834
934544	N/A	N/A	91048	91067	$^{m}C_{es}T_{eo}G_{es}T_{es}T_{es}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{es}{}^{m}C_{eo}T_{es}T_{es}A_{e}$	1835
934545	4727	4746	92150	92169	$G_{es}G_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{es}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}G_{ds}{}^{m}C_{ds}T_{es}{}^{m}C_{eo}{}^{m}C_{es}G_{es}A_{e}$	2690
934546	5073	5092	98221	98240	$^{m}C_{es}T_{eo}G_{es}G_{es}A_{es}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}A_{ds}G_{ds}G_{es}A_{eo}G_{es}{}^{m}C_{es}T_{e}$	3524
934547	N/A	N/A	91042	91061	$T_{es}{}^{m}C_{eo}A_{es}T_{es}G_{es}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{es}{}^{m}C_{eo}{}^{m}C_{es}A_{es}G_{e}$	1830
934548	541	560	13807	13826	$T_{es}A_{eo}{}^{m}C_{es}{}^{m}C_{es}T_{es}G_{ds}A_{ds}A_{ds}G_{ds}T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}A_{ds}G_{es}G_{eo}A_{es}G_{es}A_{e}$	828
934549	540	559	13806	13825	$A_{es}{}^{m}C_{eo}{}^{m}C_{es}T_{es}G_{es}A_{ds}A_{ds}G_{ds}T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}A_{ds}G_{ds}G_{es}A_{eo}G_{es}A_{es}T_{e}$	827
934552	734	753	18633	18652	$G_{es}{}^{m}C_{eo}A_{es}{}^{m}C_{es}T_{es}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{es}T_{eo}A_{es}T_{es}A_{e}$	3513
934553	737	756	18636	18655	$A_{es}A_{eo}{}^{m}C_{es}G_{es}{}^{m}C_{es}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{es}T_{eo}{}^{m}C_{es}A_{es}T_{e}$	1997
934554	738	757	18637	18656	$T_{es}A_{eo}A_{es}{}^{m}C_{es}G_{es}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{es}A_{eo}T_{es}{}^{m}C_{es}A_{e}$	2073
934555	740	759	18639	18658	$G_{es}T_{eo}T_{es}A_{es}A_{es}{}^{m}C_{ds}G_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{es}A_{eo}T_{es}A_{es}T_{e}$	2148
934556	735	754	18634	18653	$^{m}C_{es}G_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{es}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{es}A_{eo}T_{es}A_{es}T_{e}$	852
934557	736	755	18635	18654	$A_{es}{}^{m}C_{eo}G_{es}{}^{m}C_{es}A_{es}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{es}{}^{m}C_{eo}A_{es}T_{es}A_{e}$	3590
934558	N/A	N/A	19521	19540	$A_{es}G_{eo}{}^{m}C_{es}A_{es}A_{es}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C_{es}A_{eo}T_{es}A_{es}{}^{m}C_{e}$	3385
934584	7772	7791	145941	145960	$A_{es}{}^{m}C_{eo}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}T_{ds}G_{ds}A_{ds}A_{es}{}^{m}C_{eo}A_{es}T_{es}T_{e}$	1431
934585	7780	7799	145949	145968	$A_{es}T_{eo}G_{es}T_{es}G_{es}A_{ds}G_{ds}T_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{es}{}^{m}C_{eo}A_{es}T_{es}G_{e}$	1438
934586	732	751	18631	18650	$A_{es}{}^{m}C_{eo}T_{es}T_{es}A_{es}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{es}T_{eo}A_{es}A_{es}T_{e}$	3361
934587	733	752	18632	18651	$^{m}C_{es}A_{eo}{}^{m}C_{es}T_{es}T_{es}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{es}A_{eo}T_{es}A_{es}A_{e}$	3438
934588	2451	2470	62072	62091	$G_{es}T_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{es}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}G_{es}{}^{m}C_{eo}T_{es}T_{es}A_{e}$	188
934589	835	854	21666	21685	$^{m}C_{es}A_{eo}{}^{m}C_{es}T_{es}{}^{m}C_{es}A_{ds}T_{ds}G_{ds}A_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{es}{}^{m}C_{eo}A_{es}{}^{m}C_{es}A_{e}$	860
934590	836	855	21667	21686	$^{m}C_{es}{}^{m}C_{eo}A_{es}{}^{m}C_{es}T_{es}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	2757
934591	834	853	21665	21684	$A_{es}{}^{m}C_{eo}T_{es}{}^{m}C_{es}A_{es}T_{ds}G_{ds}A_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{es}A_{eo}{}^{m}C_{es}A_{es}T_{e}$	3286

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934592	2362	2381	61983	62002	$T_{es}G_{eo}{}^{m}C_{es}T_{es}{}^{m}C_{es}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{d}$ $_{s}{}^{m}C_{ds}A_{es}T_{eo}A_{es}{}^{m}C_{es}{}^{m}C_{e}$	257
934593	896	915	21727	21746	${}^{m}C_{es}T_{eo}T_{es}T_{es}{}^{m}C_{es}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}G_{ds}G_{ds}$ $G_{ds}A_{es}A_{eo}T_{es}G_{es}{}^{m}C_{e}$	291
934594	2365	2384	61986	62005	$G_{es}A_{eo}{}^{m}C_{es}T_{es}G_{es}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{d}$ $_{s}T_{ds}{}^{m}C_{es}A_{eo}{}^{m}C_{es}A_{es}T_{e}$	1017
934595	2364	2383	61985	62004	$A_{es}{}^{m}C_{eo}T_{es}G_{es}{}^{m}C_{es}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{d}$ $_{s}{}^{m}C_{ds}A_{es}{}^{m}C_{eo}A_{es}T_{es}A_{e}$	259
934596	542	561	13808	13827	$T_{es}T_{eo}A_{es}{}^{m}C_{es}{}^{m}C_{es}T_{ds}G_{ds}A_{ds}A_{ds}G_{ds}T_{ds}T_{ds}A_{ds}G_{ds}G_{d}$ $_{s}A_{es}G_{eo}G_{es}A_{es}G_{e}$	829
934597	4112	4131	86607	86626	$A_{es}G_{eo}T_{es}T_{es}T_{es}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}G_{ds}G_{ds}T_{ds}T_{ds}A_{d}$ $_{s}T_{es}A_{eo}A_{es}G_{es}G_{e}$	1172
934599	2368	2387	61989	62008	$T_{es}G_{eo}G_{es}G_{es}A_{es}{}^{m}C_{ds}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}$ $T_{ds}T_{es}{}^{m}C_{eo}T_{es}{}^{m}C_{es}A_{e}$	185
934600	2369	2388	61990	62009	$T_{es}T_{eo}G_{es}G_{es}G_{es}A_{ds}{}^{m}C_{ds}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}$ $T_{ds}T_{es}T_{eo}{}^{m}C_{es}T_{es}{}^{m}C_{e}$	1019
952334	607	626	16127	16146	$A_{es}G_{eo}T_{es}G_{es}{}^{m}C_{es}A_{ds}T_{ds}G_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}$ $A_{ds}A_{es}A_{eo}A_{es}T_{es}T_{e}$	839
952335	730	749	18629	18648	$T_{es}T_{eo}A_{es}A_{es}{}^{m}C_{es}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}T_{d}$ $_{s}A_{es}A_{eo}T_{es}{}^{m}C_{es}T_{e}$	3666
952336	872	891	21703	21722	$A_{es}T_{eo}A_{es}G_{es}{}^{m}C_{es}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}$ $C_{ds}A_{ds}A_{es}T_{eo}A_{es}T_{es}T_{e}$	1998
952338	875	894	21706	21725	$T_{es}T_{eo}{}^{m}C_{es}A_{es}T_{es}A_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C$ $_{ds}{}^{m}C_{ds}A_{es}{}^{m}C_{eo}A_{es}A_{es}T_{e}$	2149
952340	877	896	21708	21727	${}^{m}C_{es}T_{eo}T_{es}T_{es}{}^{m}C_{es}A_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{d}$ $_{s}A_{ds}{}^{m}C_{es}{}^{m}C_{eo}A_{es}{}^{m}C_{es}A_{e}$	2986
952358	3227	3246	76361	76380	$A_{es}A_{eo}G_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}A_{ds}A_{ds}A_{ds}T_{ds}G_{ds}T_{ds}G_{ds}T_{ds}{}^{m}$ $C_{ds}A_{es}A_{eo}A_{es}{}^{m}C_{es}T_{e}$	2534
952359	3228	3247	76362	76381	${}^{m}C_{es}A_{eo}A_{es}G_{es}T_{es}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{ds}A_{ds}T_{ds}G_{ds}T_{ds}G_{ds}$ $T_{ds}{}^{m}C_{es}A_{eo}A_{es}A_{es}{}^{m}C_{e}$	2610
952360	3229	3248	76363	76382	$G_{es}{}^{m}C_{eo}A_{es}A_{es}G_{es}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{ds}A_{ds}T_{ds}G_{ds}T_{ds}$ $G_{ds}T_{es}{}^{m}C_{eo}A_{es}A_{es}A_{e}$	2687
952361	3231	3250	76365	76384	$G_{es}T_{eo}G_{es}{}^{m}C_{es}A_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}A_{ds}A_{ds}T_{ds}$ $G_{ds}T_{es}G_{eo}T_{es}{}^{m}C_{es}A_{e}$	3141
952362	3498	3517	77247	77266	${}^{m}C_{es}T_{eo}T_{es}{}^{m}C_{es}A_{es}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{d}$ $_{s}G_{ds}T_{es}{}^{m}C_{eo}T_{es}{}^{m}C_{es}A_{e}$	1110
952363	3499	3518	77248	77267	$T_{es}{}^{m}C_{eo}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{d}$ $_{s}A_{ds}G_{es}T_{eo}{}^{m}C_{es}T_{es}{}^{m}C_{e}$	1111
952364	3505	3524	77254	77273	$T_{es}T_{eo}A_{es}A_{es}A_{es}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}T_{d}$ $_{s}{}^{m}C_{es}{}^{m}C_{eo}T_{es}T_{es}{}^{m}C_{e}$	1112
952365	3718	3737	82063	82082	$T_{es}G_{eo}{}^{m}C_{es}T_{es}G_{es}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}T_{ds}$ $A_{ds}A_{es}A_{eo}G_{es}A_{es}{}^{m}C_{e}$	1134
952366	3719	3738	82064	82083	$T_{es}T_{eo}G_{es}{}^{m}C_{es}T_{es}G_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}$ $T_{ds}A_{es}A_{eo}A_{es}G_{es}A_{e}$	1135
952367	3723	3742	82068	82087	$A_{es}T_{eo}{}^{m}C_{es}A_{es}T_{es}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}$ $T_{ds}A_{es}T_{eo}{}^{m}C_{es}T_{es}A_{e}$	1136
952368	4106	4125	86601	86620	$A_{es}T_{eo}T_{es}{}^{m}C_{es}G_{es}G_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}A_{ds}G_{ds}G_{ds}{}^{m}C_{d}$ $_{s}A_{es}{}^{m}C_{eo}A_{es}G_{es}{}^{m}C_{e}$	1167
952369	4107	4126	86602	86621	${}^{m}C_{es}A_{eo}T_{es}T_{es}{}^{m}C_{es}G_{ds}G_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}A_{ds}G_{ds}G_{d}$ $_{s}{}^{m}C_{es}A_{eo}{}^{m}C_{es}A_{es}G_{e}$	1168
952370	4108	4127	86603	86622	$T_{es}{}^{m}C_{eo}A_{es}T_{es}T_{es}{}^{m}C_{ds}G_{ds}G_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}A_{ds}G_{d}$ $_{s}G_{es}{}^{m}C_{eo}A_{es}{}^{m}C_{es}A_{e}$	1169
952371	4109	4128	86604	86623	$T_{es}T_{eo}{}^{m}C_{es}A_{es}T_{es}T_{ds}{}^{m}C_{ds}G_{ds}G_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}A_{d}$ $_{s}G_{es}G_{eo}{}^{m}C_{es}A_{es}{}^{m}C_{e}$	1170

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952372	4110	4129	86605	86624	$T_{es}T_{eo}T_{es}{}^{m}C_{es}A_{es}T_{ds}T_{ds}{}^{m}C_{ds}G_{ds}G_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}A_{es}G_{eo}G_{es}{}^{m}C_{es}A_{e}$	1171
952373	4111	4130	86606	86625	$G_{es}T_{eo}T_{es}T_{es}{}^{m}C_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}G_{ds}G_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{es}A_{eo}G_{es}G_{es}{}^{m}C_{e}$	235
952374	4115	4134	86610	86629	$A_{es}T_{eo}A_{es}A_{es}G_{es}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}G_{ds}G_{ds}T_{es}T_{eo}A_{es}T_{es}A_{e}$	1175
952375	608	627	16128	16147	$G_{es}A_{eo}G_{es}T_{es}G_{es}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}A_{es}A_{eo}A_{es}A_{es}T_{e}$	279
952376	609	628	16129	16148	$T_{es}G_{eo}A_{es}G_{es}T_{es}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{es}A_{eo}A_{es}A_{es}A_{e}$	840
952377	610	629	16130	16149	$A_{es}T_{eo}G_{es}A_{es}G_{es}T_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{es}A_{eo}A_{es}A_{es}A_{e}$	841
952378	611	630	16131	16150	$A_{es}A_{eo}T_{es}G_{es}A_{es}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{es}{}^{m}C_{eo}A_{es}A_{es}A_{e}$	280
952379	612	631	16132	16151	$A_{es}A_{eo}A_{es}T_{es}G_{es}A_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}{}^{m}C_{ds}A_{es}T_{eo}{}^{m}C_{es}A_{es}A_{e}$	842
952380	613	632	16133	16152	$G_{es}A_{eo}A_{es}A_{es}T_{es}G_{ds}A_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}{}^{m}C_{es}A_{eo}T_{es}{}^{m}C_{es}A_{e}$	843
952381	620	639	16140	16159	$T_{es}T_{eo}G_{es}G_{es}{}^{m}C_{es}T_{ds}G_{ds}G_{ds}A_{ds}A_{ds}A_{ds}T_{ds}G_{ds}A_{ds}G_{ds}T_{es}G_{eo}{}^{m}C_{es}A_{es}T_{e}$	844
953599	732	748	18631	18647	$T_{es}A_{eo}A_{eo}{}^{m}C_{es}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}A_{ds}Tk_{o}A_{es}A_{es}T_{e}$	3829
953600	733	749	18632	18648	$T_{es}T_{eo}A_{eo}A_{es}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}Ak_{o}T_{es}A_{es}A_{e}$	3830
953601	734	750	18633	18649	$^{m}C_{es}T_{eo}T_{eo}A_{es}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}Tk_{o}A_{es}T_{es}A_{e}$	3831
953602	735	751	18634	18650	$A_{es}{}^{m}C_{eo}T_{eo}T_{es}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}C_{ds}Ak_{o}T_{es}A_{es}T_{e}$	3832
953603	736	752	18635	18651	$^{m}C_{es}A_{eo}{}^{m}C_{eo}T_{es}T_{ds}A_{ds}A_{ds}{}^{m}C_{ds}A_{ds}A_{ds}T_{ds}A_{ds}T_{ds}{}^{m}Ck_{o}A_{es}T_{es}A_{e}$	3833
953604	1874	1890	52788	52804	$A_{es}G_{eo}{}^{m}C_{eo}A_{es}{}^{m}C_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}Tk_{o}A_{es}G_{es}{}^{m}C_{e}$	3834
953605	1791	1807	52705	52721	$A_{es}{}^{m}C_{eo}A_{eo}T_{es}T_{ds}T_{ds}{}^{m}C_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}Ck_{o}{}^{m}C_{es}A_{es}G_{e}$	3835
953606	3493	3509	77242	77258	$^{m}C_{es}{}^{m}C_{eo}T_{eo}T_{es}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}A_{ds}Gk_{o}G_{es}G_{es}G_{e}$	3836
953607	3713	3729	82058	82074	$A_{es}T_{eo}A_{eo}T_{es}{}^{m}C_{ds}T_{ds}A_{ds}A_{ds}A_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}Gk_{o}{}^{m}C_{es}A_{es}A_{e}$	3837
953608	987	1003	27962	27978	$A_{es}A_{eo}A_{eo}{}^{m}C_{es}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}Tk_{o}{}^{m}C_{es}G_{es}T_{e}$	3838
953609	4110	4126	86605	86621	$^{m}C_{es}A_{eo}T_{eo}T_{es}{}^{m}C_{ds}G_{ds}G_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}A_{ds}Gk_{o}G_{es}{}^{m}C_{es}A_{e}$	3839
953610	7775	7791	145944	145960	$A_{es}{}^{m}C_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}T_{ds}Gk_{o}A_{es}A_{es}{}^{m}C_{e}$	3840
953611	879	895	21710	21726	$T_{es}T_{eo}T_{eo}{}^{m}C_{es}A_{ds}T_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}Ak_{o}{}^{m}C_{es}{}^{m}C_{es}A_{e}$	3841
953612	834	850	21665	21681	$^{m}C_{es}A_{eo}T_{eo}G_{es}A_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}Ak_{o}{}^{m}C_{es}A_{es}T_{e}$	3842
953613	606	622	16126	16142	$^{m}C_{es}A_{eo}T_{eo}G_{es}G_{ds}{}^{m}C_{ds}A_{ds}T_{ds}{}^{m}C_{ds}A_{ds}A_{ds}A_{ds}A_{ds}Ak_{o}T_{es}T_{es}A_{e}$	3843
953614	990	1006	27965	27981	$^{m}C_{es}A_{eo}{}^{m}C_{eo}A_{es}A_{ds}A_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}G_{ds}Ak_{o}{}^{m}C_{es}T_{es}T_{e}$	3844
953615	3497	3513	77246	77262	$A_{es}G_{eo}T_{eo}T_{es}{}^{m}C_{ds}{}^{m}C_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}Tk_{o}{}^{m}C_{es}A_{es}A_{e}$	3845

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953616	4108	4124	86603	86619	$T_{es}T_{eo}{}^{m}C_{eo}G_{es}G_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{ds}A_{ds}G_{ds}G_{ds}{}^{m}Ck_{o}A_{es}{}^{m}C_{es}A_{e}$	3846
953617	1698	1714	41931	41947	$A_{es}T_{eo}T_{eo}T_{es}A_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{ds}A_{ds}T_{ds}G_{ds}A_{ds}Tk_{o}G_{es}A_{es}A_{e}$	3847

[0706]

[0707] **실시예 10: 자유 흡수를 통한 *시험관내* 인간 LRRK2 RNA 발현에서 혼합된 인터뉴클레오사이드 연결기가 있는 5-10-5 MOE 갭머의 효과**

[0708] 상기 실시예로부터 선택된 변형된 올리고뉴클레오타이드는 자유 흡수에 의해 A431 세포내 다양한 용량에서 시험되었다. 세포는, 아래 표에서 특정된 바와 같이, 0.039, 0.156, 0.625, 2.500 및 10.000 μM 농도의 변형된 올리고뉴클레오타이드로 10,000 세포/웰의 밀도에서 플레이팅되었다. 대략 24 시간의 처리 기간 후, 총 RNA는 세포로부터 단리되었고 LRRK2 RNA 수준은 정량적 실시간 PCR에 의해 측정되었다. (실시예 2에서 본 명세서에 기재된) 인간 LRRK2 프라이머 프로브 세트 RTS3132는 RNA 수준을 측정하는데 사용되었다. LRRK2 RNA 수준은, RIBOGREEN®에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다. 결과는 미처리된 대조군 세포에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다. 아래 표에서 설명된 바와 같이, LRRK2 RNA 수준은 변형된 올리고뉴클레오타이드-처리된 세포에서 용량-의존적 방식으로 감소되었다. IC50은 Prism6 소프트웨어를 사용하

는 "log(억제제) 대 반응 - 가변 경사 (4 파라미터)" 식을 사용하여 계산되었다.

표 72
자유 흡수에 의해 A431 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)					IC_{50} (μM)
	0.039 μM	0.156 μM	0.625 μM	2.500 μM	10.000 μM	
780160	101	86	56	55	48	4.5
780161	102	85	58	31	45	1.9
780164	95	75	63	52	40	3.1
780166	94	42	42	31	32	0.4
780241	70	70	46	35	50	1.3
802655	81	76	58	52	36	2.3
802665	78	73	62	59	53	14.3
802678	77	44	28	24	26	0.2
802714	84	84	64	47	40	2.8
802758	84	51	25	23	29	0.2
802770	74	68	44	28	31	0.5
802784	88	70	37	20	25	0.5
802938	109	53	50	38	34	1.0
802939	96	80	63	44	31	1.9
802963	92	102	88	78	64	26.0
803000	85	84	60	30	33	1.3
803006	89	77	53	43	37	1.7
803268	90	93	55	46	27	1.7
803270	86	80	52	44	43	2.2
872255	96	67	36	29	22	0.5
872260	52	55	33	23	29	0.1
876031	96	60	33	21	20	0.4
876180	101	94	90	90	80	>300
876190	81	68	36	24	23	0.4
876604	91	71	46	28	41	0.0
934517	80	86	43	38	48	0.9
934518	82	54	28	25	31	1.8
934523	71	49	30	15	23	0.3
934528	71	57	50	26	34	0.2
934529	76	43	24	27	29	0.4
934530	89	68	40	28	25	0.2
934553	99	73	51	33	31	0.6
934554	95	73	72	40	35	1.0
934556	63	59	41	26	28	2.1
934557	107	63	51	33	33	0.3

[0709]

[0710] **실시예 11: 붉은털 원숭이 LRRK2 RNA *시험관내*, 다중 용량에서 변형된 올리고뉴클레오타이드의 효과**

[0711] 붉은털 원숭이 LRRK2에 또한 상보성인, 상기 실시예로부터 선택된 변형된 올리고뉴클레오타이드는 LLC-MK2 원숭이 세포내 다양한 용량에서 시험되었다. 세포는, 아래 표에서 특정된 바와 같이, 20,000 세포/웰의 밀도로 플레이팅되었고 0.011, 0.034, 0.103, 0.309, 0.926, 2.778, 8.333, 및 25.000 μM 농도의 변형된 올리고뉴클레오타이드로 전기천공을 사용하여 형질감염되었다. 공지된 표적 및 서열 CCTATAGGACTATCCAGGAA (서열번호: 3848)이 없는 혼합된 포스포디에스테르 및 포스포로티오에이트 백본이 있는 5-10-5 MOE 갭머인, 대조군 올리고뉴클레오타이드, 676630은 또한 시험되었다. 대략 24 시간의 처리 기간 후, 총 RNA는 세포로부터 단리되었고 LRRK2 RNA 수준은 정량적 실시간 PCR에 의해 측정되었다. 인간 LRRK2 프라이머 프로브 세트 hLRRK2 LTS35700 (정방향 서열 CCAGGTACAATGCAAAGCTTAAT, 서열번호: 20으로서 본 명세서에 지정됨; 역방향 서열 TCAGTCCAATCACTGACAAGTT, 서열번호: 21로서 본 명세서에 지정됨; 프로브 서열 TTGGGAAGTCCTTGGTGTTCACCA, 서열번호: 22로서 본 명세서에 지정됨)은 RNA 수준을 측정하는데 사용되었다. LRRK2 RNA 수준은, RIBOGREEN에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다 결과는 미처리된 대조군 세포에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다. 아래 표에서 설명된 바와 같이, LRRK2 RNA 수준은 변형된 올리고뉴클레오타이드-처리된 세포에서 용량-의존적 방식으로 감소되었다. IC50은 Prism6 소프트웨어를 사용하는 "log(억제제) 대 반응 - 가변 경사 (4

파라미터)" 식을 사용하여 계산되었다.

표 73
LLC-MK2 붉은털 원숭이 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)								IC_{50} (μM)
	0.011 μM	0.034 μM	0.103 μM	0.309 μM	0.926 μM	2.778 μM	8.333 μM	25.000 μM	
676630	118	114	124	128	123	134	125	125	n/a#
780241	114	118	116	92	67	51	46	41	6.4
802714**	122	116	130	131	112	80	41	20	7.4
803268*	101	109	105	112	108	89	76	69	50.4
876031	122	113	106	84	46	14	8	1	0.9
876604**	97	95	99	97	107	107	105	77	n/a#
934556	88	84	71	55	30	12	11	6	0.3

#IC_{50} 값은 계산될 수 없다
*이 변형된 올리고뉴클레오타이드는 붉은털 원숭이 LRRK2 핵산 서열 번호: 3 에 상보성이고 상기에 1 개의 미스매치를 함유한다
**이들 변형된 올리고뉴클레오타이드는 붉은털 원숭이 LRRK2 핵산 서열 번호: 3 에 상보성이고 상기에 2 개의 미스매치를 함유한다

[0712]

[0713] **실시예 12: 인간 LRRK2 RNA 발현 *시험관내*, 다중 용량에서 변형된 올리고뉴클레오타이드의 효과**

[0714] 상기 기재된 변형된 올리고뉴클레오타이드는 SH-SY5Y 세포내 다양한 용량에서 시험되었다. 세포는, 아래 표에서 특정된 바와 같이, 20,000 세포/웰의 밀도로 플레이팅되었고 0.011, 0.034, 0.103, 0.309, 0.926, 2.778, 8.333, 및 25.000 μM 농도의 변형된 올리고뉴클레오타이드로 전기천공을 사용하여 형질감염되었다. 공지된 표적이 없는 혼합된 포스포디에스테르 및 포스포로티오에이트 백본이 있는 5-10-5 MOE 갭머인, 대조군 올리고뉴클레오타이드, 676630은 또한 시험되었다. 대략 24 시간의 처리 기간 후, 총 RNA는 세포로부터 단리되었고 LRRK2 RNA 수준은 정량적 실시간 PCR에 의해 측정되었다. (실시예 11에서 본 명세서에 기재된) 인간 LRRK2 프라이머 프로브 세트 LTS35700은 RNA 수준을 측정하는데 사용되었다. LRRK2 RNA 수준은, RIBOGREEN에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다 결과는 미처리된 대조군 세포에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다. 아래 표에서 설명된 바와 같이, LRRK2 RNA 수준은 변형된 올리고뉴클레오타이드-처리된 세포에서 용량-의존적 방식으로 감소되었다. IC50은 Prism6 소프트웨어를 사용하는 "log(억제제) 대 반응 - 가변 경사 (4 파라미터)" 식을 사용하여 계산되었다.

표 74
SH-SY5Y 세포에서 인간 LRRK2 발현의 용량-의존적 감소

화합물 번호	LRRK2 발현 (% 대조군)								IC_{50} (μM)
	0.011 μM	0.034 μM	0.103 μM	0.309 μM	0.926 μM	2.778 μM	8.333 μM	25.000 μM	
대조군 676630	129	113	108	133	109	131	122	133	n/a*
780241	117	104	92	93	76	59	58	58	n/a*
802714	100	123	98	93	75	56	44	36	6.3
803268	99	121	96	83	77	84	73	68	105.6
876031	96	99	93	73	49	22	18	15	1.0
876604	97	91	78	65	43	20	15	15	0.6
934556	97	90	77	55	42	27	20	15	0.6

*IC_{50} 값은 계산될 수 없다

[0715]

[0716] **실시예 13: 형질전환 마우스에서 인간 LRRK2에 상보성인 변형된 올리고뉴클레오타이드의 활성, 2주 평가**

[0717] 상기 기재된 변형된 올리고뉴클레오타이드는 2주 후 활성을 평가하기 위해 인간 BAC 야생형 LRRK2 형질전환 마우스 모델 B6;SJL-Tg(LRRK2)66Mjff/J; Stock No: 013725, The Jackson Laboratory)에서 시험되었다. BAC *LRRK2-Wt* 이식유전자에 대하여 반접합성인 마우스는 생존성 및 가임성이다. 이들 마우스는 BAC 이식유전자 상에서 인간 *LRRK2* 프로모터/인핸서 영역에 의해 유도된 야생형 인간 류신-풍부 반복 키나제 2 (*LRRK2*) 유전자를 발현시킨다 (Ouyang Y 등, 2011). 이 모델로부터 마우스는, 척수 및 뇌를 포함하는, 다양한 조직에서 인간 LRRK2를 발현시킨다.

[0718] *처리*

[0719] LRRK2 형질전환 마우스 각각은 아래 표에서 열거된 300㎍의 변형된 올리고뉴클레오타이드의 단일 뇌혈관내(ICV) 용량을 받았다. 각 처리 그룹은 4마리 마우스로 이루어졌다. 4마리 마우스의 그룹은 음성 대조군으로서 PBS를 받았다.

[0720] *RNA 분석*

[0721] 2주 후, 마우스는 희생되었고, RNA는 (실시예 11에서 상기 본 명세서에 기재된) 프라이머 프로브 세트 hLRRK2 LTS35700을 사용하여 LRRK2의 RNA 발현의 측정의 실시간 PCR 분석을 위하여 피질 뇌 조직 및 척수로부터 추출되었다. 결과는, 사이클로필린 A로 정규화된, PBS 대조군에 비하여 에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다.

[0722] 아래 표에서 나타난 바와 같이, 변형된 올리고뉴클레오타이드에 의한 처리는 PBS 대조군에 비교하여 인간 LRRK2 RNA의 감소를 초래하였다.

표 75

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
693430	46	37
725607	24	50
725608	19	33
725609	30	37
780162	59	76
780164	27	62
780166	14	26
780189	58	49
780202	42	36
780203	65	66
780205	13	29
780219	34	43
780236	19	29
780241	23	38
780243	54	47
780254	42	41
780284	61	53
780321	39	64
780347	42	51
780549	63	53
780602	93	103
780620	47	45
780624	63	75

[0723]

780649	52	48
780685	42	37
802655	30	48
802678	7	26
802685	38	32
802686	17	40
802688	18	27
802689	16	36
802731	42	44
802746	42	64
802747	56	44
802748	32	25
802845	30	26
802846	35	41
802848	68	72

표 76

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
802849	78	77
802850	73	92
802888	49	63
802911	80	92
802915	54	68
802935	69	61
802936	40	52

[0724]

802937	43	40
802958	57	78
802960	54	48
802961	34	44
802962	40	51
802974	50	55
803002	30	44
803003	67	85
803004	73	86
803005	66	65
803046	95	65
803065	55	52
802959	41	62
803075	38	54
803102	89	89
803112	40	51
803122	52	71
803386	73	80
803515	81	104
803516	63	81
803517	55	67
803518	60	85
803519	70	79
803520	50	80
803571	66	71
803595	80	71
803604	65	67
803629	57	72
803682	47	46

[0725]

803744	47	53
803770	73	54
803771	53	46
803773	40	50
803782	80	96

표 77
형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
780160	13	15
780161	24	30
802665	17	35
802678	27	35
802690	33	40
802714	21	47
802758	23	42
802770	11	22
802781	32	49
802784	16	30
802938	21	32
802939	13	41
802963	26	51
803000	22	42
803001	36	50
803006	29	39
803268	31	52
803269	38	49

[0726]

803270	24	75
803271	31	48
803272	76	75
803273	77	70
803274	50	65

표 78
형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
802678	24	19
803275	52	77
872246	44	49
872247	57	63
872248	24	44
872249	61	73
872250	34	28
872251	37	51
872252	54	62
872253	29	43
872254	94	71
872256	34	44
872257	70	72
872258	55	42
872259	82	72
872260	10	30
872261	37	55
872262	50	71

[0727]

872263	28	49
872264	43	67
872265	36	35
872266	92	88
872267	68	74

표 79

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
802678	9	19
802780	42	49
802847	54	64
803021	67	70
803045	36	60
803064	42	67
803123	56	76
803181	41	74
803470	34	52
803503	67	72
803665	58	84
803769	71	90
872255	23	42
872268	52	66
872269	37	54
872270	39	61
872271	94	101

[0728]

872272	76	77
872273	31	38
872274	54	85
872275	84	84
872276	73	97
872277	47	67
872278	36	68
872279	39	69
874144	81	86
874145	64	67
874146	67	64
874147	78	79
874148	57	58
874149	55	69
874150	57	44
874151	102	84

표 80

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
802678	30	41
803426	70	63
872280	83	64
872281	49	64
872282	48	64
872283	61	60

[0729]

872285	26	41
876019	58	72
876097	47	46
876141	47	50
876168	103	89
876180	21	27
934558	54	49
934584	45	55
934585	162	95
934586	174	102
934587	35	238
934588	30	42
934589	19	30
934590	24	50
934591	42	52
934592	38	49
934593	31	35
934594	22	45
934595	59	61
934596	n.d.	n.d.
934597	48	59
934600	15	33

표 81

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
780241	55	57

[0730]

802678	12	20
876185	59	56
876190	25	38
876223	46	70
876326	36	57
876345	77	79
876735	64	57
876766	67	75
876900	41	46
877068	44	52
877159	52	61
877305	52	57
877328	68	76
890207	42	60
890208	32	45
890209	40	58
934599	29	37

표 82

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
802678	15	21
803427	34	32
876028	99	61
876029	106	69
876043	55	36
876062	39	26

[0731]

876074	70	35
876146	82	42
876189	54	34
876203	90	46
876221	60	31
876237	80	35
876262	58	31
876284	74	41
876287	129	57
876302	81	34
876303	76	46
876899	60	34
876960	93	41
877119	62	36
877171	67	66
877292	68	58
877326	74	58
877349	106	81
877395	69	75

표 83

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
802678	13	13
876027	166	94
876031	23	18

[0732]

876042	85	60
876068	80	54
876088	48	60
876143	79	70
876186	60	45
876195	54	48
876261	32	35
876263	46	42
876282	64	45
876285	89	59
876294	37	39
876301	51	55
876328	63	53
876604	26	22
876790	87	54
877098	65	41
877176	175	74

표 84

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
802678	31	40
872284	69	57
876274	65	60
877113	76	98
877303	67	68
890206	41	77

[0733]

934538	49	49
934540	80	67
934541	43	54
934542	44	63
934543	58	60
934544	46	52
934545	39	35
934546	37	44
934547	45	51
934548	37	43
934549	34	42
934552	37	35
934553	27	36
934554	23	36
934555	38	43
934556	10	17
934557	17	29
934558	46	51

표 85

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
802678	10	17
934514	17	28
934515	16	21
934516	9	26

[0734]

934517	16	36
934518	25	23
934519	71	70
934520	47	27
934521	52	50
934522	45	58
934523	29	30
934524	35	38
934525	50	56
934526	41	43
934528	28	33
934529	30	33
934530	31	35
934531	33	37
934532	33	37
934533	37	32
934534	38	44
934535	80	55
934536	57	61
934537	45	45

표 86

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
802678	11	22
952334	43	27

[0735]

952335	86	96
952336	34	53
952338	68	62
952340	36	36
953599	123	87
953600	105	83
953601	103	87
953602	70	89
953603	48	74
953604	36	46
953605	69	51
953606	93	74
953607	53	65
953608	41	36
953609	84	69
953610	59	61
953611	42	61
953612	47	85
953613	81	74
953614	61	62
953615	41	42
953616	79	57
953617	107	67

[0736]

표 87
형질전환 마우스에서 인간 LRRK2 RNA의 감소

화합물 번호	LRRK2 발현 (% 대조군)	
	대뇌피질	척수
PBS	100	100
802678	16	18
952358	80	84
952359	54	66
952360	34	39
952361	51	47
952362	42	41
952363	45	42
952364	45	57
952365	39	63
952366	38	56
952367	61	50
952368	33	52
952369	56	59
952370	37	62
952371	34	56
952372	27	65
952373	43	55
952374	58	72
952375	20	42
952376	29	41
952377	20	34
952378	28	41
952379	35	49

[0737]

952380	22	51
952381	22	40

[0738]

[0739] **실시예 14: 형질전환 마우스에서 인간 LRRK2에 상보성인 변형된 올리고뉴클레오타이드의 활성, 8주 평가**

[0740] 상기 기재된 변형된 올리고뉴클레오타이드는 8주 후 활성을 평가하기 위해 인간 BAC 야생형 LRRK2 형질전환 마우스 모델에서 시험되었다. BAC *LRRK2-Wt* 이식유전자에 대하여 반접합성인 마우스는 생존성 및 가임성이다. 이들 마우스는 BAC 이식유전자 상에서 인간 *LRRK2* 프로모터/인핸서 영역에 의해 유도된 야생형 인간 류신-풍부 반복 키나제 2 (*LRRK2*) 유전자를 발현시킨다 (Ouyang Y 등, 2011). 이 모델로부터 마우스는, 척수 및 뇌를 포함하는, 다양한 조직에서 인간 LRRK2를 발현시킨다.

[0741] *처리*

[0742] LRRK2 형질전환 마우스 각각은 아래 표에서 열거된 300μg의 변형된 올리고뉴클레오타이드의 단일 ICV 용량을 받았다. 각 처리 그룹은 4마리 마우스로 이루어졌다. 4마리 마우스의 그룹은 음성 대조군으로서 PBS를 받았다.

[0743] *RNA 분석*

[0744] 8주 후, 마우스는 희생되었고, RNA는 (실시예 11에서 상기 본 명세서에 기재된) 프라이머 프로브 세트 hLRRK2 LTS35700을 사용하여 LRRK2의 RNA 발현의 측정의 실시간 PCR 분석을 위하여 피질 뇌 조직 및 척수로부터 추출되었다. 결과는, 사이클로필린 A로 정규화된, PBS 대조군에 비하여 에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다.

[0745] 아래 표에서 나타난 바와 같이, 변형된 올리고뉴클레오타이드에 의한 처리는 PBS 대조군에 비교하여 인간 LRRK2 RNA의 감소를 초래하였다.

표 88

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	대뇌피질내 LRRK2 발현 (% 대조군)
PBS	100
802665	44
934556	16
934517	26
802678	19
876031	33
934553	34
934554	34
780166	28
802714	27
802770	16
802938	23
803270	33
780161	39
780241	44
934557	18

표 89

형질전환 마우스에서 인간 LRRK2 RNA 의 감소

화합물 번호	대뇌피질내 LRRK2 발현 (% 대조군)
PBS	100
780164	54
803000	39

[0746]

803268	66
876604	78
934518	21

[0747]

[0748] **실시예 15: 형질전환 랫트에서 인간 LRRK2에 상보성인 변형된 올리고뉴클레오타이드의 활성**

[0749] 상기 기재된 변형된 올리고뉴클레오타이드는 활성을 평가하기 위해 인간 BAC G2019S 돌연변이체 LRRK2 형질전환 랫트 (NTac:SD-Tg(LRRK*G2019S)571Cjli; Taconic) 모델에서 시험되었다. 모델은 NTac:SD 접합체속에 G2019S를 가진 전체 인간 LRRK2 유전자의 전핵 주사를 통해 창작되었다. 이 모델로부터 랫트는, 척수 및 뇌를 포함하는 다양한 조직에서 인간 LRRK2를 발현시킨다 (West AB 등, *J. Comp. Neurology,* 2014, 522(11):2465-2480).

[0750] *처리*

[0751] LRRK2 형질전환 랫트 각각은 아래 표에서 열거된 1,000㎍의 변형된 올리고뉴클레오타이드의 단일 ICV 용량을 받았다. 각 처리 그룹은 4-5마리 랫트로 이루어졌다. 4마리 랫트의 그룹은 음성 대조군으로서 PBS를 받았다.

[0752] *RNA 분석*

[0753] 2주 후, 랫트는 희생되었고, RNA는 (실시예 11에서 상기 본 명세서에 기재된) 프라이머 프로브 세트 hLRRK2 LTS35700을 사용하여 LRRK2의 RNA 발현의 측정의 실시간 PCR 분석을 위하여 뇌간, 피질 뇌 조직, 척수, 폐 및 신장으로부터 추출되었다. 결과는, 사이클로필린 A로 정규화된, PBS 대조군에 비하여 에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다.

[0754] 아래 표에서 나타난 바와 같이, 변형된 올리고뉴클레오타이드에 의한 처리는 PBS 대조군에 비교하여 인간 LRRK2 RNA의 감소를 초래하였다.

표 90

형질전환 랫트에서 인간 LRRK2 RNA 의 감소

화합물 번호	LRRK2 발현 (% 대조군)		
	뇌간	대뇌피질	척수
PBS	100	100	100
780241	60	42	54
802714	43	33	53
803268	66	58	73
876031	33	9	33
876604	38	19	39
934556	31	9	35

[0755]

[0756] **실시예 16: 형질전환 랫트에서 인간 LRRK2에 상보성인 변형된 인터뉴클레오사이드의 효력**

[0757] 상기 기재된 변형된 올리고뉴클레오타이드는, 올리고뉴클레오타이드의 효력을 시험하기 위해, 상기 본 명세서에 기재된, 인간 BAC G2019S 돌연변이체 LRRK2 형질전환 랫트 (NTac:SD-Tg(LRRK*G2019S)571Cjli) 모델에서 시험되었다.

[0758] *처리*

[0759] LRRK2 형질전환 랫트 각각은 아래 표에서 열거된 10, 30, 100, 300, 700, 1,000, 또는 3,000 ㎍의 변형된 올리고뉴클레오타이드의 단일 뇌혈관내 (ICV) 용량을 받았다. 각 처리 그룹은 5마리 랫트로 이루어졌다. 5마리 랫트의 그룹은 각 투약 그룹에 대하여 음성 대조군으로서 PBS를 받았다.

[0760] *RNA 분석*

[0761] 2주 후, 랫트는 희생되었고 RNA는 (실시예 11에서 상기 본 명세서에 기재된) 프라이머 프로브 세트 hLRRK2 LTS35700을 사용하여 LRRK2의 RNA 발현의 측정의 실시간 PCR 분석을 위하여 대뇌피질로부터 추출되었다. 결과는, 사이클로필린 A로 정규화된, PBS 대조군에 비하여 에 비하여 퍼센트 LRRK2 RNA 수준으로서 아래 표에서 제시된다.

[0762] 아래 표에서 나타난 바와 같이, 변형된 올리고뉴클레오타이드에 의한 처리는 PBS 대조군에 비교하여 인간 LRRK2 RNA의 감소를 초래하였다. 용량 반응 데이터는 GraphPad Prism 6 소프트웨어 (San Diego, CA)를 사용하여 분석되었다. ED_{50} 값은, 하기 제약조건: ED_{50}에 대하여 최하부 > 0, 최상부 = 100, F = 50이 있는, GraphPad 식

"log(아고니스트) 대 반응 -- Find ECanything"에서 만들어진 것을 이용하여 log 전환된 용량 또는 농도 그리고 개별 동물 LRRK2 RNA 수준으로부터 계산되었다.

표 91

형질전환 랫트, 대뇌피질에서 인간 LRRK2 RNA의 용량-의존적 퍼센트 감소

화합물 번호	대뇌피질내 LRRK2 발현 (% 대조군)						ED_{50} (μg/g)
	10 μg	30 μg	100 μg	300 μg	1000 μg	3000 μg	
780241	107.4	96.4	75.9	41.9	33.1	34.9	129
876031	102.0	94.6	67.6	18.7	5.9	4.6	135
934556	105.9	94.2	56.6	17.3	7.1	3.7	111

[0763]

[0764] **실시예 17: 야생형 마우스에서 LRRK2에 상보성인 변형된 올리고뉴클레오타이드의 내성, 3 시간 FOB 평가**

[0765] 상기 기재된 변형된 올리고뉴클레타이드는 올리고뉴클레오타이드의 내성을 평가하기 위해 야생형 암컷 C57/B16 마우스에서 시험되었다. 야생형 암컷 C57/B16 마우스 각각은 아래 표에서 열거된 700 μg의 변형된 올리고뉴클레오타이드의 단일 ICV 용량을 받았다. 각 처리 그룹은 4마리 마우스로 이루어졌다. 4마리 마우스의 그룹은 (아래 별도 표에서 확인된) 각 실험용 음성 대조군으로서 PBS를 받았다. 3 시간 후기-주사에서, 마우스는 7개의 상이한 기준에 따라 평가되었다. 기준은 (1) 마우스가 활발하고, 민첩하고 반응성이었음; (2) 마우스가 자극 없이 서있거나 움츠렸음; (3) 마우스가 자극 없이 어떤 움직임을 보여주었음; (4) 마우스가 들어올린 후 전방 움직임을 나타냈음; (5) 마우스가 들어올린 후 어떤 움직임을 보여주었음; (6) 마우스가 꼬리 핀칭에 반응하였음; (7) 정상 호흡이다. 7개의 기준 각각에 대하여, 마우스는 기준을 충족시켰다면 0 그리고 그렇지 않았다면 1의 서브스코어 (기능적 관찰 배터리 스코어 또는 FOB)가 제공되었다. 모두 7개의 기준이 평가된 후, 스코어는 각 마우스에 대하여 합계되었고 각 처리 그룹 내에서 평균되었다. 결과는 아래 표에서 제시된다.

표 92

700 μg 용량에서 마우스내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
802678	0
693430	0
725607	0
780164	0
780166	6
780205	0
780254	7
780321	0
780685	2
802685	0
802688	0
802689	0
802731	6
802746	6
802888	6
802936	4
802937	4
802959	1
802962	0
802974	0
803002	7
803075	4
803682	1

표 93

700 μg 용량에서 마우스내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
780160	0
802784	6
802939	3
803006	5

[0766]

872248	7
872253	7
872260	7
872263	7
876190	2
934552	2
934553	0
934554	2
934555	2
934556	1
934557	1

표 94

700 μg 용량에서 마우스내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
872255	5
934514	4
934515	2
934516	6
934518	4
934523	7
934528	5
934529	5
934530	3
934517	4
802758	7
876180	0

표 95

700 μg 용량에서 마우스내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
780161	1
780164	5
780166	6

[0767]

802665	1
802714	3
802770	4
802938	4
802963	0
803000	4
803268	4
803270	1

표 96

700 μg 용량에서 마우스내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
876031	0
876604	5

표 97

700 μg 용량에서 마우스내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
952334	2
952335	0
952336	2
952338	5
952340	3
952358	5
952359	7
952360	6
952361	4
952362	6
952363	3

표 98

700 μg 용량에서 마우스내 내성 스코어

[0768]

화합물 번호	3 시간 FOB
PBS	0
952364	0
952365	0
952366	3
952367	6
952368	5
952369	7
952370	7
952371	6
952372	7
952373	7
952374	4
952375	2
952376	5
952377	6
952378	3
952379	4
952380	7
952381	6
953599	0
953600	0
953601	0
953602	0
953603	0
953604	4
953605	5
953606	6
953607	3
953608	6
953609	6
953610	3
953611	3
953612	1
953613	0
953614	2
953615	4

[0769]

953616	5
953617	5

[0770]

[0771] **실시예 18: 랫트에서 인간 LRRK2에 상보성인 변형된 올리고뉴클레오타이드의 내성, 3시간 FOB 평가**

[0772] 상기 기재된 변형된 올리고뉴클레오타이드는 올리고뉴클레오타이드의 내성을 평가하기 위해 스프라그 돌리 랫트에서 시험되었다. 스프라그 돌리 랫트 각각은 아래 표에서 열거된 3 mg의 올리고뉴클레오타이드의 단일 척수내(IT) 용량을 받았다. 각 처리 그룹은 3-4마리 랫트로 이루어졌다. 4마리 랫트의 그룹은 (아래 별도 표에서 확인된) 각 실험용 음성 대조군으로서 PBS를 받았다. 3 시간 후기-주사에서, 바디의 7개 상이한 부위의 움직임은 각 랫트에 대하여 평가되었다. 7개의 바디 부위는 (1) 랫트의 꼬리; (2) 랫트의 뒷태; (3) 랫트의 뒷다리; (4) 랫트의 뒷발; (5) 랫트의 앞발; (6) 랫트의 앞태; (7) 랫트의 두부이다. 7개의 상이한 바디 부위의 각각에 대하여, 각 랫트는 바디 부위가 움직이고 있었다면 0 그리고 바디 부위가 움직이지 않았다면 1의 서브-스코어가 제공되었다. 7개 기준의 각각에 대하여, 랫트는 상기 기준을 충족시키면 0 또는 바디 부위가 그렇지 않으면 1의

서브스코어 (기능적 관찰 배터리 스코어 또는 FOB)가 제공되었다. 모두 7개의 기준이 평가된 후, 스코어는 각 랫트에 대하여 합계되었고 각 처리 그룹 내에서 평균되었다. 결과는 아래 표에서 제시된다.

표 99
3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	n.d.
780164	2
780166	2
780189	1
780236	4
780241	1
780243	3
780254	3
780347	0
780549	0

표 100
3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0.25
780236	5
802678	2
802688	2
802748	6
872259	3
872261	4
872269	4
872279	3

표 101
3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
725607	1
780620	6
802888	5
802936	5

[0773]

802937	5
802959	4
802961	2
802962	2
802974	3
803520	5

표 102
3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
725609	0
780164	3
780166	6
780205	3
802689	2
802731	7
802746	5
802845	2
802846	4
876088	1

표 103
3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
802655	5
802686	2
802688	2
803075	5
803682	1
876031	0
876261	4
876263	2
876294	2

[0774]

표 104
3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
693430	3
780219	5
780254	2
780321	3
780347	1

표 105
3 mg 용량에서 랫트내 내성 스코에스

화합물 번호	3 시간 FOB
PBS	0
780160	1
780161	2
802784	5
802938	1
802939	3
802963	2
803000	5
803006	4
803270	1
872248	3
872253	6

표 106
3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
872260	5
872263	7
934553	0
934554	0

[0775]

934555	2
934556	0
934557	0

표 107
3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
934517	2
934523	6
934528	4
934529	1
934530	0

표 108
3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
802678	0.5
802758	3.25
876604	5

표 109
3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
802665	1
802714	2
802770	2
803268	3
872255	5
934516	3
934518	4

[0776]

표 110

3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
693421	2.5
690093	3.0

표 111

3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
952334	4
952335	2
952336	3
952338	2
952358	3
952359	2

표 112

3 mg 용량에서 랫트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
952378	5
952379	5
952380	3
952381	4
953599	1
953600	1
953601	0
953602	2
953603	0
953604	3
953605	5
953606	5

[0777]

표 113
3 mg 용량에서 탯트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
953607	3
953608	4
953609	5
953610	3
953611	4
953612	3
953613	1
953614	4
953615	1
953616	4
953617	4

표 114
3 mg 용량에서 탯트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
952371	4
952372	4
952373	4
952374	2
952375	5
952376	4
952377	5

표 115
3 mg 용량에서 탯트내 내성 스코어

화합물 번호	3 시간 FOB
PBS	0
952340	1
952360	4

[0778]

952361	3
952362	5
952363	4
952364	5
952365	2
952366	5
952367	5
952368	6
952369	4
952370	5

[0779]

[0780] **실시예 19: PFF 모델에서 변형된 올리고뉴클레오타이드에 의한 LRRK2의 예방적 감소**

[0781] 야생형 마우스는 PBS 비히클 단독 또는 아래 표에서 열거된 700 μg의 올리고뉴클레오타이드의 단일 ICV 주사를 받았다. 각 처리 그룹은 11 또는 12마리 마우스로 이루어졌다. 올리고뉴클레오타이드 처리 2주 후, α-시누클레인의 사전형성된 피브릴 (PFFs)는, 기재된 바와 같이, 몇몇 뇌 영역에서 α-시누클레인 응집체의 형성 및 운동

장해를 초래하는, 선조체속에 주사되었다 (*참고* Luk 등, *Science*, 2012, *338*, 949-953). 하나의 대조군 그룹은 PFFs의 주사를 받지 않았다. 올리고뉴클레오타이드 처리 55일 후, 운동 기능은 와이어 행 시험에서 시험되었다. 결과는 각 처리 그룹의 마우스가 와이어상에 남아있었던 시간의 평균 기간으로서 아래 표에서 제시된다.

[0782] 와이어 행 시험 1일 후, 각 처리 그룹에서 모든 마우스는 올리고뉴클레오타이드 및 PFF 주사를 받지 않았던 그룹을 제외하고 희생되었고; 그 그룹에서 단지 4마리 마우스는 희생되었다. 동물은 빙냉된 PBS로 관류되었다. 동측성 반구는 고정되었고 면역화학을 위하여 가공되었다. 대측성 중뇌 및 선조체는 RNA 분석때까지 절개 및 동결되었고, 반면 전체 대측성 대뇌피질은 단백질 분석때까지 절개 및 동결되었다. LRRK2 RNA 발현은 쥣과 프라이머 프로브 세트 RTS3043 (정향방 서열 GGCGAGTTATCCGCACCAT, 서열번호: 23으로서 본 명세서에 지정됨; 역방향 서열 CCAAAACCAGCATGACATTCTTAA, 서열번호:24로서 본 명세서에 지정됨; 프로브 서열 TGAGAGCCATGGCCACAGCACAA, 서열번호: 25로서 본 명세서에 지정됨)을 사용하여 정량적 실시간 PCR에 의해 분석되었다. LRRK2 RNA 수준은, RIBOGREEN에 의해 측정된 바와 같이, 총 RNA 함량에 따라 조정되었다. 결과는 올리고뉴클레오타이드 처리도 PFF 주사도 받지 않았던 야생형 대조군 그룹에 비하여 평균 퍼센트 억제로서 아래 표에서 나타난다.

[0783] 대뇌피질에서 LRRK2, α-시누클레인, 및 과인산화된 α-시누클레인 (p-α-syn) 단백질 수준은 웨스턴 블랏에 의해 분석되었다. 대측성 대뇌피질 조직은 RIPA 완충액에서 먼저 균질화되었고 13,300x g에서 원심분리되었다. 상청액은 LRRK2 단백질 수준에 대하여 웨스턴 블랏 처리되었고, β-튜불린은 장입 대조군으로서 사용되었다. 결과는 대뇌피질에서 LRRK2 단백질 수준이 올리고뉴클레오타이드 처리를 받지 않았던 동물에서보다 올리고뉴클레오타이드 처리된 동물에서 상당히 더 낮았음을 나타냈다. 펠렛은 RIPA 완충액에서 재현탁되었고, 100,000x g에서 원심분리되었고, 생성된 불용성 물질은 2% SDS 완충액에서 추가로 현탁되었고, 이어서 추가로 100,000x g 회전되었다. 생성된 상청액은 α-시누클레인 및 p-α-syn에 대하여 웨스턴 블랏에 의해 분석되었다. 결과는 PFF 주사가, Luk 등에서 보고된 바와 같이, 불용성 응집체속에 내인성 마우스 α-시누클레인의 동원을 초래하였음을 보여주었다. 응집체는 또한 과인산화되었다. 올리고뉴클레오타이드 처리는, 웨스턴 블랏에서 불용성 마우스 α-시누클레인 및 p-α-syn의 감소에 의해 증명된 바와 같이, 응집체의 형성을 감소시켰다. 흑질에서 p-α-syn 응집체는 면역조직화학에 의해 가시화되었다. 각 처리 그룹으로부터 각 크기의 샘플에 대하여 관찰된 응집체의 평균 수는 아래 표에서 나타난다. 결과의 1원 ANOVA 시험은 PBS 처리된 동물과 올리고뉴클레오타이드 처리된 동물 사이 차이가 유의미하였음을 보여주었다.

표 116
LRKK2 변형된 올리고뉴클레오타이드에 의한 PFF 마우스의 예방적 처리

화합물 번호	주사된 PFF	와이어 행 시험의 시간 (초)	LRRK2 RNA 의 억제 (%)		p-α-syn 응집체의 수
			중뇌	선조체	
PBS	무	193	0	4.0	0
PBS	유	94	0	0	42
693421	유	187	52.0	49.0	12
690093	유	175	43.0	24.8	21

[0784]

[0785] **실시예 20: PFF 모델에서 변형된 올리고뉴클레오타이드에 의한 LRRK2의 감소**

[0786] PFFs의 주사후 야생형 마우스에서 올리고뉴클레오타이드 감소의 효과는 690093을 사용하여 평가되었다. 마우스는 올리고뉴클레오타이드 처리가 PFF 주사 2주 전 대신에 PFF 주사 2주 후 발생하였음을 제외하고 실시예 19에서 기재된 바와 같이 처리되었다. 각 처리 그룹은 10마리 동물로 이루어졌다. PFF 주사 55일 후, 마우스는, 실시예 19에서 기재된 바와 같이, 와이어 행 시험에서 평가되었다. 와이어 행 시험 1일 후, 마우스는 희생되었고, 중뇌, 선조체, 및 흑질은 수집되었고, 실시예 19에서 기재된 바와 같이, LRRK2 RNA 및 p-α-syn 응집체는 측정되었다. 결과는 각 처리 그룹에 대한 평균으로서 아래 표에서 나타난다. "nd"의 기재는 데이터가 그 처리 그룹에 대하여 수집되지 않았음을 나타낸다. 결과는 변형된 올리고뉴클레오타이드가 PFF 모델의 개시 후 투여된 경우 조차, 운동 기능이 개선되었고 병리적 응집체가 감소되었음을 보여준다.

표 117
LRKK2 변형된 올리고뉴클레오타이드에 의한 PFF 마우스의 처리

올리고 ID	주사된 PFF	와이어 행 시간의 시간 (초)	LRRK2 RNA 의 억제 (%)		p-α-syn 응집체의 수
			중뇌	선조체	
PBS	무	227	0	0	nd
PBS	유	58	0	0	49
690093	유	141	62.3	43.6	38

[0787]

[0788] **실시예 21: 장기 연구에서 PFF 모델에서 변형된 올리고뉴클레오타이드에 의한 LRRK2의 예방적 감소**

[0789] 변형된 올리고뉴클레오타이드는 변형된 올리고뉴클레오타이드에 의한 장기 처리가 도파민작용성 뉴런을 보호하는지를 결정하기 위해 장기 연구에서 시험되었다. 흑질 치밀부에서 α-syn 응집체의 축적은 경시적으로 도파민작용성 뉴런의 생존을 손상시킨다 (Luk 2012, Tran 2014).

[0790] PFFs의 주사후 야생형 마우스에서 올리고뉴클레오타이드 감소의 효과는 공지된 표적이 없이 혼합된 포스포디에스테르 및 포스포로티오에이트 백본을 가진 5-10-5 MOE 갭머인, 대조군 올리고뉴클레오타이드 676630 또는 690093을 사용하여 평가되었다. 마우스는 90일에 690093의 제2 ICV 용량을 마우스가 받았던 것을 제외하고 실시예 19에서 기재된 바와 같이 처리되었고, 제1 ICV 처리 후 180일에 희생되었다. 각 처리 그룹은 12마리 동물로 이루어졌다. 희생에서, 중뇌, 선조체, 및 흑질은 수집되었고, LRRK2 RNA 및 p-α-syn 응집체는, 실시예 19에서 기재된 바와 같이, 측정되었고, 도파민작용성 세포는 항-티로신 수산화효소 (TH) 항체를 사용하여 면역조직화학에 의해 정량화되었다. 결과는 각 처리 그룹에 대하여 평균으로서 아래 표에서 나타난다. 결과는, LRRK2에 상보성인 변형된 올리고뉴클레오타이드로 처리된 그룹에서, 병리적 응집체의 수가 장기 처리 과정 동안 감소되었음을 보여준다. 추가적으로, TH-양성 뉴런의 정량화는 690093-매개된 LRRK2 억압이 대조군 처리된 세포에 비교된 경우 동측성 흑질 치밀부에서 TH-양성 세포를 구제하였음을 보여주었다.

표 118
장기 연구에서 LRKK2 변형된 올리고뉴클레오타이드에 의한 PFF 마우스의 예방적 처리

화합물 번호	주사된 PFF	LRRK2 RNA 의 억제 (%)		p-α-syn 응집체의 수	도파민작용성 세포의 수
		중뇌	선조체		
676630	유	0	0	160	5880
690093	유	61.7	0	48	7522

[0791]

[0792] **실시예 22: 랫트에서 인간 LRRK2에 상보성인 변형된 올리고뉴클레오타이드의 내성, 장기 평가**

[0793] 동일 조건 하에서 실시된 별도 연구에서, 상기 기재된 변형된 올리고뉴클레오타이드는 올리고뉴클레오타이드의 장기 내성을 평가하기 위해 스프라그 돌리 랫트에서 시험되었다. 스프라그 돌리 랫트 각각은 3mg의 올리고뉴클레오타이드 또는 PBS의 단일 척수내 (IT) 전달된 용량을 받았다. 1주 후기-처리를 시작하는 6주 동안, 각 동물은 유해 효과에 대하여 훈련된 관찰자에 의해 매주 칭량되었고 평가되었다. 유해 효과는, 비제한적으로, 하기를 포함하는 PBS-처리된 대조군 동물에서 전형적이지 않은 신경학적 기능장애로서 정의되었다: 비정상 사지 벌어짐, 비정상 걸음걸이, 떨림, 비정상 호흡, 마비, 및 경직. 유해 효과의 개시는 기능장애가 먼저 기록된 경우 후기-투약하는 주로서 정의된다. 유해 효과가 달성되지 않았다면, 개시는 없다 (-). 유해 효과의 개시는 전형적으로 PBS-처리된 동물과 유사한 체중 증가/유지의 부족에 의해 정의된 바와 같이 번창하지 못함과 상관관계가 있다. 유사한 내성 평가는 하기에서 기재되었다: Ostergaard 등, Nucleic Acids Res. 2013 Nov; 41(21): 9634-9650 및 Southwell 등, Mol Ther. 2014 Dec; 22(12): 2093-2106. 아래 표에서 나타난 바와 같이, 876031, 780241, 802714, 803268, 876604, 및 934556은 장기 내성 평가에서 양호하게 용인되었다.

표 119

3 mg 용량에서 랫트내 장기 내성

화합물 번호	유해 효과 개시, 후기-처리 주, 개체 동물
690093	2, 3, 4, 4
693421	4, -, -, -
876031	-,-,-,-
780241	-,-,-,-
802714	-,-,-,-
803268	-,-,-,-
876604	-,-,-,-
934556	-,-,-,-
PBS	-,-,-,-

[0794]

[0795] 본 개시내용은 하기 비제한 번호로 매겨진 청구범위를 제공한다.

서 열 목 록

SEQUENCE LISTING

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<120> COMPOUNDS AND METHODS FOR REDUCING LRRK2 EXPRESSION

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<150> 62/690,790

<151> 2018-06-27

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agtcaggctg aacaatgtcc aggaaggaaa acagatagaa acgctggtcc aaatcctgga 240

ggatctgctg gtgttcacgt actccgagca cgcctccaag ttatttcaag gcaaaaatat 300

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