



(19) 대한민국특허청(KR)
(12) 공개특허공보(A)

(11) 공개번호 10-2017-0086027
(43) 공개일자 2017년07월25일

- (51) 국제특허분류(Int. Cl.)
A61K 35/741 (2014.01) A61K 9/00 (2006.01)
C12Q 1/68 (2006.01)
- (52) CPC특허분류
A61K 35/741 (2013.01)
A61K 9/0053 (2013.01)
- (21) 출원번호 10-2017-7012563
- (22) 출원일자(국제) 2015년10월28일
심사청구일자 없음
- (85) 번역문제출일자 2017년05월10일
- (86) 국제출원번호 PCT/US2015/057888
- (87) 국제공개번호 WO 2016/069792
국제공개일자 2016년05월06일
- (30) 우선권주장
62/072,917 2014년10월30일 미국(US)

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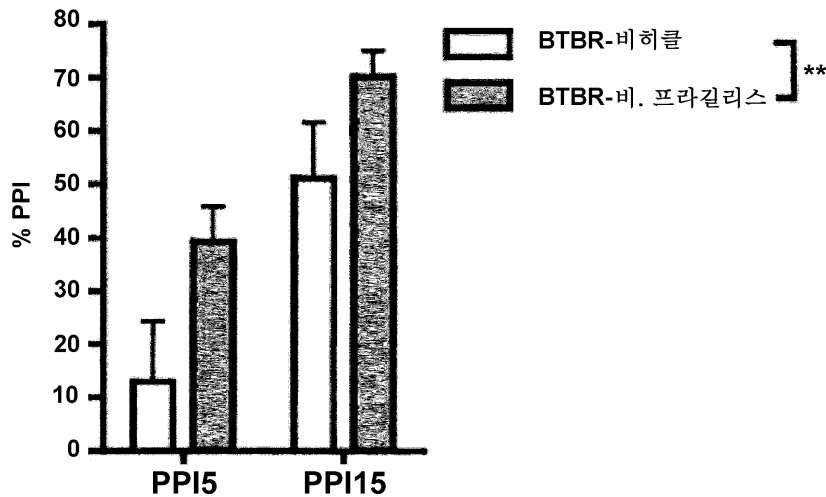
전체 청구항 수 : 총 21 항

(54) 발명의 명칭 신경발달 장애에서의 행동을 개선시키기 위한 박테리아를 포함하는 조성물 및 방법

(57) 요약

하나 이상의 자폐 스펙트럼 장애 (ASD) 또는 간질의 치료를 필요로 하는 대상체에서의 하나 이상의 자폐 스펙트럼 장애 (ASD) 또는 간질의 치료에서 사용하기 위한 프로바이오틱이 일부 실시양태에서 제공된다. 이러한 프로바이오틱은 박테로이데스(*Bacteroides*) 박테리아 (예를 들어, 비. 프라길리스(*B. fragilis*))를 포함할 수 있다. 일부 실시양태에서, 행동 증상 및 임의적인 유전자 마커의 조합을 기초로 대상체가 ASD 또는 간질의 치료를 필요로 하는 것으로 확인된다. 치료 시, 대상체에서 하나 이상의 ASD-관련 행동이 개선된다.

대표도 - 도1c



(52) CPC특허분류
C12Q 1/6883 (2013.01)

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명세서

청구범위

청구항 1

대상체에게 유효량의 하나 이상의 박테로이데스 박테리아를 투여하는 단계를 포함하는, 자폐 스펙트럼 장애 (ASD), 간질, 또는 피질 형성이상 국소 간질이 있는 대상체에서 행동 수행을 개선하기 위한 방법.

청구항 2

제1항에 있어서,

대상체의 샘플에서 하기 중 적어도 하나의 기능 상실의 존재 또는 부재를 검출하는 단계:

컨택틴(contactin) 연관 단백질-유사 2 (CNTNAP2); 및

정신분열병에서 파괴됨 1 (Disc1); 및

대상체에 CNTNAP2 및 Disc1 중 적어도 하나의 기능 상실이 있으면 대상체에게 유효량의 하나 이상의 박테로이데스 박테리아를 투여하는 단계

를 추가로 포함하는 방법.

청구항 3

제1항 또는 제2항에 있어서, 유효량의 하나 이상의 박테로이데스 박테리아가 비. 프라길리스(*B. fragilis*)를 포함하는 것인 방법.

청구항 4

제1항 내지 제3항 중 어느 한 항에 있어서, 유효량의 하나 이상의 박테로이데스 박테리아가 비. 프라길리스, 비. 세타이오타오미크론(*B. thetaiotaomicron*), 비. 불가투스(*B. vulgatus*), 또는 열거된 박테리아 중 2개 또는 3개의 혼합물을 포함하는 것인 방법.

청구항 5

제1항 내지 제4항 중 어느 한 항에 있어서, 개선되는 행동 수행이 언어 이해, 언어 산출, 사교성, 의사소통, 감각운동 게이팅, 불안, 또는 반복 행동 중 적어도 하나를 포함하는 것인 방법.

청구항 6

제1항 내지 제5항 중 어느 한 항에 있어서, 개선되는 행동 수행이 불안, 감각운동 게이팅, 및 사교성 중 적어도 하나를 포함하는 것인 방법.

청구항 7

제1항 내지 제6항 중 어느 한 항에 있어서, 방법에서 대상체에게 투여되는 단독 활성 성분이 본질적으로 하나 이상의 박테로이데스 박테리아로 이루어지는 것인 방법.

청구항 8

제1항 내지 제7항 중 어느 한 항에 있어서, 유효량의 하나 이상의 박테로이데스 박테리아가 하나 이상의 박테로이데스 박테리아 이외의 박테리아가 실질적으로 없는 조성물 내에 있는 것인 방법.

청구항 9

제1항 내지 제8항 중 어느 한 항에 있어서, CNTNAP2 또는 Disc1의 기능 상실의 존재 또는 부재를 검출하는 단계가 CNTNAP2 단백질 또는 Disc1 단백질을 코딩하는 유전자의 대립유전자를 검출하는 것을 포함하는 것인 방법.

청구항 10

제1항 내지 제9항 중 어느 한 항에 있어서, CNTNAP2 또는 Disc1의 기능 상실의 존재 또는 부재를 검출하는 단계가 CNTNAP2 또는 Disc1 폴리펩티드의 존재 또는 부재를 검출하는 것을 포함하는 것인 방법.

청구항 11

제1항 내지 제10항 중 어느 한 항에 있어서, CNTNAP2 또는 Disc1의 기능 상실의 존재 또는 부재를 검출하는 단계가 대상체의 샘플에 수행되는 것인 방법.

청구항 12

제1항 내지 제10항 중 어느 한 항에 있어서, CNTNAP2 또는 Disc1의 기능 상실의 존재 또는 부재를 검출하는 단계가 생체 내에서 대상체에 수행되는 것인 방법.

청구항 13

제1항 내지 제12항 중 어느 한 항에 있어서, CNTNAP2 또는 Disc1의 기능 상실의 존재 또는 부재를 검출하는 단계가 CNTNAP2 또는 Disc1을 코딩하는 유전자의 적어도 일부분의 결실을 검출하는 것을 포함하는 것인 방법.

청구항 14

제1항 내지 제13항 중 어느 한 항에 있어서, 대상체가 불안, 자폐 스펙트럼 장애 (ASD), 또는 ASD의 증상 중 하나 이상이 있는 병리학적 상태를 앓는 것인 방법.

청구항 15

제1항 내지 제15항 중 어느 한 항에 있어서, 유효량의 하나 이상의 박테로이데스 박테리아가 대상체에게 경구로 투여되는 것인 방법.

청구항 16

인간 대상체에게 투여하기에 적절한, 하나 이상의 박테로이데스 박테리아를 포함하는 조성물; 및
 하기 중 적어도 하나:

컨택틴 연관 단백질-유사 2 (CNTNAP2)를 코딩하는 유전자, 또는 정신분열병에서 파괴됨 1 (Disc1)을 코딩하는 유전자에 대해 실질적으로 상보적인 핵산; 또는
 CNTNAP2, 또는 Disc1 폴리펩티드에 특이적으로 결합하는 항체를 포함하는 키트.

청구항 17

제16항에 있어서, 조성물이 경구 투여에 적절한 것인 키트.

청구항 18

제16항 또는 제17항에 있어서, 하나 이상의 박테로이데스 박테리아가 비. 프라길리스를 포함하는 것인 키트.

청구항 19

제16항 내지 제18항 중 어느 한 항에 있어서, 조성물이 본질적으로 하나 이상의 박테로이데스 박테리아로 이루어지는 것인 키트.

청구항 20

제16항 내지 제19항 중 어느 한 항에 있어서, 조성물에 박테로이데스 프라길리스, 비. 세타이오타오미크론, 및 비. 불가투스 이외의 박테리아가 실질적으로 없는 것인 키트.

청구항 21

제16항 내지 제20항 중 어느 한 항에 있어서, 조성물에 박테로이데스 프라길리스 이외의 박테리아가 실질적으로 없는 것인 키트.

발명의 설명

기술 분야

- [0001] 관련 출원에 대한 상호 참조
- [0002] 본 출원은 2014년 10월 30일에 출원된 미국 가출원 번호 62/072,917을 우선권 주장하고, 이는 이에 의해 전문이 참조로 포함된다.
- [0003] 연방 정부 지원 R&D에 관한 진술
- [0004] 본 발명은 미국 육군이 수여 번호 W81XWH-11-1-0515 하에 수여하고, 미국 국립 보건원(National Institutes of Health)이 수여 번호 GM099535 & NS074374 & MH090749 하에 수여한 정부 지원으로 이루어졌다. 정부는 본 발명에 특정 권리를 갖는다.
- [0005] 서열 목록에 관한 참조
- [0006] 2015년 10월 27일에 생성되고 크기가 556,368 바이트인 파일명 CALTE113WOSEQUENCE.TXT의 전자 서열 목록이 본 출원과 함께 제출된다. 전자 서열 목록 내의 정보는 이에 의해 전문이 참조로 포함된다.

배경 기술

- [0007] 배경
- [0008] 자폐 스펙트럼 장애 (ASD)는 반복 행동 및 사회적 상호작용 및 의사소통에서의 결손을 수반하는 파괴적인 질병일 수 있다. 미국에서 백만 명이 ASD로 추정된다. 놀랍게도, 지난 수십 년 동안 ASD 진단이 증가하여, 이를 매우 눈에 띄는 공중 보건 우려이게 한다. ASD에서의 유전적 및 환경적 위험 요인 양쪽 모두의 기여를 뒷받침하는 것이 증가하고 있다.
- [0009] 분야
- [0010] 본원에 기술된 일부 실시양태는, 일반적으로, 자폐 스펙트럼 장애 (ASD) 증상 및/또는 간질 증상을 치료하는데 사용될 수 있는 프로바이오틱 조성물에 관한 것이다.

발명의 내용

- [0011] 개요
- [0012] 본원에 기술된 일부 실시양태에 따라, 자폐증, 간질, 또는 피질 형성이상 국소 간질이 있는 대상체에서 행동 수행을 개선하기 위한 방법이 제공된다. 이러한 방법은 자폐 스펙트럼 장애 (ASD), 간질, 또는 피질 형성이상 국소 간질이 있는 대상체에게 유효량의 하나 이상의 박테로이데스 박테리아를 투여하는 단계를 포함할 수 있다. 일부 실시양태에서, 이러한 방법은 대상체의 샘플에서 컨택틴(contactin) 연관 단백질-유사 2 (CNTNAP2) 및 정신분열병에서 파괴됨 1 (Disc1) 중 적어도 하나의 기능 상실의 존재 또는 부재를 검출하는 단계를 추가로 포함한다. 이러한 방법은 대상체에 CNTNAP2 및 Disc1 중 적어도 하나의 기능 상실이 있으면 대상체에게 유효량의 하나 이상의 박테로이데스 박테리아를 투여하는 단계를 추가로 포함할 수 있다. 일부 실시양태에서, 유효량의 하나 이상의 박테로이데스 박테리아는 비. 프라길리스(*B. fragilis*)를 포함한다. 일부 실시양태에서, 유효량의 하나 이상의 박테로이데스 박테리아는 비. 프라길리스, 비. 세타이오타오미크론(*B. thetaiotaomicron*), 비. 불가투스(*B. vulgatus*), 또는 열거된 박테리아 중 2개 또는 3개의 혼합물을 포함한다. 일부 실시양태에서, 개선되는 행동 수행은 언어 이해, 언어 산출, 사교성, 의사소통, 감각운동 게이팅, 불안, 또는 반복 행동 중 적어도 하나를 포함한다. 일부 실시양태에서, 개선되는 행동 수행은 불안, 감각운동 게이팅, 및 사교성 중 적어도 하나를 포함한다. 일부 실시양태에서, 방법에서 대상체에게 투여되는 단독 활성 성분은 본질적으로 하나 이상의 박테로이데스 박테리아로 이루어진다. 일부 실시양태에서, 유효량의 하나 이상의 박테로이데스 박테리아는 하나 이상의 박테로이데스 박테리아 이외의 박테리아가 실질적으로 없는 조성물 내에 있다. 일부 실시양태에서, CNTNAP2 또는 Disc1의 기능 상실의 존재 또는 부재를 검출하는 단계는 CNTNAP2 단백질 또는 Disc1 단백질을 코딩하는 유전자의 대립유전자를 검출하는 것을 포함한다. 일부 실시양태에서, CNTNAP2 또는 Disc1의 기능 상실

의 존재 또는 부재를 검출하는 단계는 CNTNAP2 또는 Disc1 폴리펩티드의 존재 또는 부재를 검출하는 것을 포함한다. 일부 실시양태에서, CNTNAP2 또는 Disc1의 기능 상실의 존재 또는 부재를 검출하는 단계는 대상체의 샘플에 수행된다. 일부 실시양태에서, CNTNAP2 또는 Disc1의 기능 상실의 존재 또는 부재를 검출하는 단계는 생체 내에서 대상체에 수행된다. 일부 실시양태에서, CNTNAP2 또는 Disc1을 코딩하는 유전자의 적어도 일부분의 결실을 검출하는 것을 포함한다. 일부 실시양태에서, 대상체는 불안, 자폐 스펙트럼 장애 (ASD), 또는 ASD의 증상 중 하나 이상이 있는 병리학적 상태를 앓는다. 일부 실시양태에서, 유효량의 하나 이상의 박테로이데스 박테리아는 대상체에게 경구로 투여된다. 일부 실시양태에서, 이러한 방법은 대상체를 ASD, 간질, 또는 피질 형성이상 국소 간질 중 적어도 하나가 있는 것으로 확인하는 단계를 추가로 포함한다. 일부 실시양태에서, 유효량의 하나 이상의 박테로이데스 박테리아는 적어도 약 10^7 콜로니 형성 단위 (cfu), 예를 들어 적어도 약 10^7 cfu, 적어도 약 10^8 cfu, 적어도 약 10^9 cfu, 적어도 약 10^{10} cfu, 적어도 약 10^{11} cfu, 또는 적어도 약 10^{12} cfu를 포함한다.

[0013] 본원에 기술된 일부 실시양태에 따라, 키트가 제공된다. 키트는 인간 대상체에게 투여하기에 적절한, 하나 이상의 박테로이데스 박테리아를 포함하는 조성물을 포함할 수 있다. 키트는 컨택틴 연관 단백질-유사 2 (CNTNAP2)를 코딩하는 유전자, 또는 정신분열병에서 파괴됨 1 (Disc1)을 코딩하는 유전자에 대해 실질적으로 상보적인 핵산; 또는 CNTNAP2 또는 Disc1 폴리펩티드에 특이적으로 결합하는 항체 중 적어도 하나를 포함할 수 있다. 일부 실시양태에서, 조성물은 경구 투여에 적절하다. 일부 실시양태에서, 하나 이상의 박테로이데스 박테리아는 비. 프라길리스를 포함한다. 일부 실시양태에서, 조성물은 본질적으로 하나 이상의 박테로이데스 박테리아로 이루어진다. 일부 실시양태에서, 조성물에 박테로이데스 프라길리스, 비. 세타이오타오미크론, 및 비. 불가투스 이외의 박테리아가 실질적으로 없다. 일부 실시양태에서, 조성물에 박테로이데스 프라길리스 이외의 박테리아가 실질적으로 없다. 일부 실시양태에서, 조성물은 적어도 약 10^7 콜로니 형성 단위 (cfu)의 박테로이데스 박테리아, 예를 들어 적어도 약 10^7 cfu, 적어도 약 10^8 cfu, 적어도 약 10^9 cfu, 적어도 약 10^{10} cfu, 적어도 약 10^{11} cfu, 또는 적어도 약 10^{12} cfu의 박테로이데스 박테리아를 포함한다.

도면의 간단한 설명

[0014] 도면의 간단한 설명

도 1a-f는 본원에 기술된 일부 실시양태에 따라 BTBR 및 CNTNAP2 마우스에서의 여러 ASD-관련 행동이 비. 프라길리스에 의해 수정된다는 것을 도시하는 일련의 그래프이다. 본원에 기술된 일부 실시양태에 따라 개방 공간 진입 (도 1a); 구슬 물기 (도 1b); 프리펄스(prepulse) 억제 (PPI) (도 1c); 개방 공간 이동 거리 (cm) (도 1d); 개방 공간 속도 (cm/s) (도 1e); 및 털손질 테스트 (도 1f)에 대해 평가된 비. 프라길리스 처치 마우스 및 대조군 마우스에 대한 데이터를 도시하는 그래프가 제시된다.

발명을 실시하기 위한 구체적인 내용

[0015] 상세한 설명

[0016] 하기의 상세한 설명에서, 본원의 일부를 형성하는 첨부된 도면이 참조된다. 도면에서, 문맥적으로 달리 지시되지 않는 한, 전형적으로 유사 기호로 유사 성분이 확인된다. 상세한 설명, 도면 및 청구항에 기술된 예시적인 실시양태는 제한적인 것으로 의도되지 않는다. 본원에서 제시된 주제의 취지 또는 범주를 벗어나지 않으면서, 다른 실시양태가 이용될 수 있고, 다른 변화가 이루어질 수 있다. 일반적으로 본원에 기술되고 도면에 도해된 바와 같은 본 개시내용의 측면들이 광범위한 상이한 구성으로 배열, 교체, 조합, 분리 및 설계될 수 있고, 이들 모두가 명시적으로 본원에서 구상된다는 것이 쉽게 이해될 것이다.

[0017] 유전적 및 환경적 위험 요인 양쪽 모두가 자폐 스펙트럼 장애 (ASD)에 기여할 수 있는 것으로 본원에서 생각된다. 본원에 기술된 다양한 실시양태에 따라, 특정 위험 요인 또는 증상 조합이 있는 대상체에서 ASD 증상을 치료 또는 예방하기 위한 방법, 용도, 조성물 및 키트가 제공된다. 특정한 유전자 마커 및/또는 증상 조합이 있는 대상체가 ASD 및/또는 간질 증상의 치료를 필요로 하는 것으로, 그리고 추가로 본원에 기술된 일부 실시양태에 따른 프로바이오틱으로의 치료를 위한 후보로서 확인될 수 있는 것으로 추가로 생각된다. 컨택틴 연관 단백질-유사 2 (CNTNAP2) 또는 정신분열병에서 파괴됨 1 (DISC1) 중 하나 이상의 돌연변이가 있는 것으로 확인된 대상체는 신경발달 장애, 예를 들어 ASD 또는 간질의 위험이 있을 수 있다. 박테로이데스 박테리아를 포함하는 유효량의 프로바이오틱이 ASD 증상 및/또는 간질 증상을 치료 또는 예방하도록 대상체에게 투여될 수 있다.

- [0018] 임신 동안의 중증 감염 후에 태어난 아동에서 ASD 비율이 더 높다는 것을 나타내는 대형 역학적 연구에 의해 입증되는 바와 같이, ASD에 대한 실질적인 환경 위험은 모체 감염이다. 유사한 연관이 임신 동안의 모체 혈청 또는 양수 내의 상승된 시토카인 및 케모카인으로 발견되었다. 자폐증 대상체로부터의 척수액 및 뇌의 분석에서, 대조군과 비교하여 활성화된 미세아교세포 및 상승된 염증유발성 시토카인, 뿐만 아니라 뇌 및 주변부에서의 면역-관련 유전자의 조절곤란이 밝혀졌다. 또한, 유의한 비율의 ASD 대상체가 변비, 복부 통증, 면역 활성화 및 장 장벽 기능장애 ("장 누수")를 포함하는 위장 (GI) 이상을 앓는다. 이러한 비-신경학적 특색과 일관되게, 최근의 연구가 대조군과 비교하여 ASD 아동에서 장 박테리아의 조성 (장 마이크로바이옴(microbiome))이 변경된다는 것을 나타냈고, 이는 GI 합병증이 있는 이에서 악화되는 특색이다. 총괄적으로, ASD에서의 잠재적인 장-면역-뇌 연관성을 시사하는 증거가 증가하고 있다.
- [0019] 마우스 및 비-인간 영장류의 모체 면역계의 활성화가 ASD에서 발견되는 핵심적인 행동 결손 및 신경 이상을 나타내는 자손을 초래한다는 것이 본원에서 기술된다. 어떠한 이론에 의해서도 제한되지 않으면서, 마우스의 마이크로바이옴이 모체 면역 활성화 (MIA) 후 변경되는 것으로 생각된다. 본원에 기술된 일부 실시양태에 따라, 인간 마이크로바이옴으로부터의 프로바이오틱인 박테로이데스 프라길리스가 마우스 모델에서 면역 활성화, ASD-관련 행동 결손 및/또는 피질 형성이상 국소 간질을 호전시킬 수 있다. 어떠한 이론에 의해서도 제한되지 않으면서, 장 박테리아가 ASD와 관련된 유전자-환경 상호작용을 조정하는 것에서 실질적인 역할을 하는 것으로 생각된다.
- [0020] 후보 인간 유전자를 기초로 ASD의 여러 마우스 모델이 있지만, 컨택틴 연관 단백질-유사 2 (CNTNAP2) 녹아웃 (knockout) 마우스가 특히 흥미로운데, 연관성(association), 연관(linkage), 유전자 발현 및 영상화 데이터가 ASD에서의 이러한 유전자의 공통 및 희귀 변이체의 역할을 뒷받침하기 때문이다. 특히, ASD에서 언어 결손에 대한 위험을 증가시키는 동일한 CNTNAP2 변이체가 인간 대상체에서 비정상적인 기능적 뇌 연결성에 이른다. 또한 CNTNAP2 마우스는 피질 형성이상 국소 간질에 특이적인 행동을 모델링한다. BTBR T⁺ tfl J 모델은 CNTNAP2-/- 마우스에 대해 상보적인데, ASD의 3가지 핵심 행동을 나타내는 근교계이기 때문이다. 추가로, BTBR 마우스는 선천 면역 반응이 상승된 것으로 나타났다. BTBR 모델은 DISC1 유전자의 기능 상실을 포함한다.
- [0021] 비. 프라길리스 처치를 CNTNAP2 및 BTBR 마우스에서 테스트하였다. 비. 프라길리스 처치가 CNTNAP2-/- 마우스에서 과다활동 및 증가된 자가-털손질 (반복 행동)을 수정하는 것으로 본원에서 나타난다 (도 1d-f). 또한, 비. 프라길리스가 BTBR 마우스에서 불안, 반복 행동 및 놀람 반응을 호전시킨다 (도 1a-c).
- [0022] 도 1a-c에 나타난 바와 같이, 박테로이데스 박테리아인 비. 프라길리스를 BTBR 자폐증 모델 마우스에 투여하는 것이 불안-유사 행동을 호전시키고 (중앙 공간 진입에 의해 측정됨; 도 1a 참조), 반복 행동을 호전시키며 (구슬 문기에 의해 측정됨; 도 1b 참조), 감각운동 게이팅에서의 결손을 호전시킨다 (프리펠스 억제 테스트에 의해 측정됨; 도 1c 참조). 따라서, 본원에 개시된 일부 실시양태에서, BTBR 모델에 상응하는 증상 및/또는 유전적 배경이 있는 인간 대상체에게 박테로이데스 박테리아를 투여하는 것을 포함하는 방법 및 용도가 ASD 증상을 치료 및/또는 예방할 수 있다. BTBR 모델에서 개선되는 행동에 상응하여, 일부 실시양태에서, 대상체는 감각운동 게이팅에서의 결손, 손상된 사교성, 및/또는 불안이 있는 것으로 확인되고, 박테로이데스 박테리아를 포함하거나, 이로 이루어지거나 또는 본질적으로 이로 이루어지는 유효량의 프로바이오틱이 투여되어, 지시된 행동을 치료 또는 개선한다. 일부 실시양태에서, 대상체는 BTBR의 유전적 배경에 상응하는 돌연변이, DISC1에서의 돌연변이가 있는 것으로 확인되고, 박테로이데스 박테리아를 포함하거나, 이로 이루어지거나 또는 본질적으로 이로 이루어지는 유효량의 프로바이오틱이 투여되어, ASD 행동을 치료 또는 개선한다.
- [0023] 도 1d-f에 나타난 바와 같이, 박테로이데스 박테리아인 비. 프라길리스를 CNTNAP2 자폐증 모델 마우스에 투여하는 것이 개방 공간 이동 거리 (도 1d) 및 개방 공간 속도 (도 1e)에 의해 측정되는 바와 같은 과다활동 행동의 호전, 및 반복 행동의 호전 (자가-털손질 테스트에 의해 측정됨; 도 1f 참조)을 초래한다. 따라서, 본원에 기술된 일부 실시양태에서, 박테로이데스 박테리아를 포함하거나, 이로 이루어지거나 또는 본질적으로 이로 이루어지는 프로바이오틱을 CNTNAP2 모델에 상응하는 증상 및/또는 유전적 배경이 있는 인간 대상체에게 투여하는 것을 포함하는 방법 및 용도가 ASD 증상 및/또는 간질 (예를 들어 피질 형성이상 국소 간질 증상)을 치료 및/또는 예방할 수 있다. CNTNAP2 모델에서 개선되는 행동에 상응하여, 일부 실시양태에서, 대상체는 하기의 행동 결손 중 적어도 하나가 있는 것으로 확인된다: 결손성 의사소통 행동 (예를 들어, 결손성 언어 산출 및/또는 이해, 결손성 사교성, 및 또는 결손성 의사소통), 결손성 감각운동 게이팅 행동, 증가된 불안 행동, 과다활동 행동 및/또는 반복 행동. 대상체에게 박테로이데스 박테리아를 포함하거나, 이로 이루어지거나 또는 본질적으로 이로 이루어지는 유효량의 프로바이오틱이 투여되어, 지시된 행동을 치료 또는 개선할 수 있다. 일부 실시양태

에서, 대상체는 CNTNAP2에서의 돌연변이가 있는 것으로 확인되고, 박테로이데스 박테리아를 포함하거나, 이로 이루어지거나 또는 본질적으로 이로 이루어지는 유효량의 프로바이오틱이 투여되어, CNTNAP2이 위험 요인인 적어도 하나의 행동을 개선 또는 예방한다. 임의적으로, 대상체는 CNTNAP2에서의 기능 상실 돌연변이에 대해 동형 접합성인 것으로 확인된다. 임의적으로, 대상체는 CNTNAP2에서의 기능 상실 돌연변이에 대해 이형접합성인 것으로 확인된다. 임의적으로, 프로바이오틱은 엔테로코쿠스 박테리아를 추가로 포함한다.

[0024] 호모 사피엔스(*Homo sapiens*)의 컨택틴-연관 단백질-유사 2 (CNTNAP2) 유전자는 척추동물 신경계에서 세포 부착 분자 및 수용체로서 기능하는 뉴렉신(neurexin) 패밀리의 구성원으로서 확인되는 생성물을 코딩한다. 호모 사피엔스 CNTNAP2 유전자는 7번 염색체 상의 세포유전학 위치 7q35에서 2 Mb의 DNA에 걸쳐지는 것으로 확인된다. 진뱅크(Genbank) 등록 번호 AH010723으로서 입수가능한 호모 사피엔스 CNTNAP2 유전자에 대한 부분적인 코딩 서열 (CDS), 및 상응하는 기준 서열이 서열식별번호(SEQ ID NO): 1에서 제공된다. 일부 실시양태에서, 대상체는 CNTNAP2 유전자에서의 기능 상실 돌연변이가 있는 것으로 확인된다. 본원에서 사용된 바와 같이, "기능 상실" 돌연변이는 광범위하게 사용되고, 하이포모르프(hypomorphic) 돌연변이, 무효(null) 돌연변이, 및 우성 음성 돌연변이를 포함한다. 본원에 기술된 일부 실시양태에 따른 CNTNAP2에서의 "기능 상실 돌연변이"의 비제한적인 예는 CNTNAP2 유전자 생성물의 기능을 방해하는 점 돌연변이, CNTNAP2 발현을 감소시키거나 제거하는 조절 요소 예컨대 프로모터 또는 인핸서의 돌연변이, CNTNAP2 전체 또는 이의 일부의 결실, 또는 이의 임의의 조합을 포함한다.

[0025] 호모 사피엔스의 "정신분열병에서 파괴됨 1" (DISC1) 유전자는 핵, 세포질 및 미토콘드리아에 위치하는, 다중 코일드 코일(coiled coil) 모티프가 있는 단백질을 코딩하는 것으로 확인되었다. DISC1이 코딩하는 단백질은 다른 단백질과의 상호작용을 통해 신경돌기 성장 및 피질 발달에 수반된다. DISC1은 정신분열병, 우울증, 및 양극성 장애를 포함하는 가족형 행동 장애와 연관되고, 뉴런의 기능을 포함하는 다수의 세포 기능에 관여하는 단백질을 코딩하며, BTBR 모델에서 돌연변이된다. 호모 사피엔스 DISC1 유전자는 1번 염색체의 세포유전학 위치 1q42.1에 존재하는 것으로 확인된다. 진뱅크 등록 번호 NG_011681에서 DISC1의 서열을 입수할 수 있다. DISC1의 기준 서열이 서열식별번호: 2로서 제공된다. 본원에서의 실시양태에 따른 DISC1에서의 "기능 상실 돌연변이"의 비제한적인 예는 DISC1 유전자 생성물의 기능을 방해하는 점 돌연변이, DISC1 발현을 감소시키거나 제거하는 조절 요소 예컨대 프로모터 또는 인핸서의 돌연변이, DISC1 전체 또는 이의 일부의 결실, DISC1 유전자좌를 파괴하는 염색체 전위, 예컨대 t(1;11)(q42.1;q14.3), 및 이의 임의의 조합을 포함한다.

[0026] 본원에 개시된 유전자 중 임의의 것의 서열, 또는 이러한 유전자에서의 다형성의 존재를 관련 기술 분야의 통상의 기술자에게 공지된 방법, 예를 들어 폴리머라제 연쇄 반응, 핵산 시퀀싱, 마이크로어레이 분석, 핵산 프로브에 대한 친화력, 원위치 혼성화 등을 사용하여 확인할 수 있다. 일부 실시양태에서, 식별된 유전자 중 임의의 것에서의 다형성의 존재 또는 부재를, 예를 들어 야생형 유전자 생성물에 대해 특이적인 항체 또는 유전자 생성물의 돌연변이체 아이소형에 대해 특이적인 항체를 사용하여, 야생형 유전자 생성물의 존재 또는 부재를 식별함으로써 확인할 수 있다.

[0027] **정의**

[0028] 달리 정의되지 않는 한, 본원에서 사용된 기술 및 과학 용어는 본 개시내용이 속하는 분야의 통상의 기술자가 통상적으로 이해하는 바와 동일한 의미를 갖는다. 예를 들어, 문헌 [Singleton et al., Dictionary of Microbiology and Molecular Biology 2nd ed., J. Wiley & Sons (New York, NY 1994)]; [Sambrook et al., Molecular Cloning, A Laboratory Manual, Cold Springs Harbor Press (Cold Springs Harbor, NY 1989)]을 참조한다. 본 개시내용의 목적을 위해, 하기의 용어들이 아래에서 정의된다.

[0029] 본원에서 사용된 바와 같이, 용어 "대상체"는 척추동물, 예컨대 포유동물이다. 용어 "포유동물"은 포유강에 속하는 개체로서 정의되고, 비제한적으로, 인간, 가축 및 농장 동물, 및 동물원, 스포츠 또는 애완 동물, 예컨대 양, 개, 말, 고양이 또는 소를 포함한다. 일부 실시양태에서, 대상체는 인간이다. 일부 실시양태에서, 대상체는 비-인간 영장류이다.

[0030] 본원에서 사용된 바와 같이, 용어 "상태/장애/증상" 또는 "행동 이상"은 불안, 유약 X, 레트 증후군, 결절 경화증, 강박 장애, 주의력 결핍 장애, 정신분열병, 간질 (예를 들어, 피질 형성이상 국소 간질), 자폐 장애 (고진적 자폐증), 아스퍼거 장애 (아스퍼거 증후군), 상세불명의 전반적 발달 장애 (PDD-NOS), 소아기 붕괴성 장애 (CDD), 또는 ASD 증상 중 하나 이상이 있는 병리학적 상태를 포함하지만 이에 제한되지 않는, 대상체가 나타내는 증상을 지칭한다.

[0031] 본원에서 사용된 바와 같이, 용어 "치료를 필요로 하는 대상체"는 상기 언급된 행동 장애/증상 중 하나 이상을 나타내거나 앓는 대상체를 지칭한다. 일부 실시양태에서, 치료를 필요로 하는 대상체는 정신분열병, ASD, 간질 (예를 들어, 피질 형성이상 국소 간질), 또는 ASD 또는 간질과 연관된 위장 또는 면역학적 병리 (예를 들어, 장 누수 증후군) 중 하나 이상을 앓는다. 표준 행동 테스트 프로토콜/가이드라인을 사용하여 적격자가 이같은 치료를 필요로 하는 개체를 확인할 수 있다. 동일한 행동 테스트 프로토콜/가이드라인을 개체의 장애 및/또는 증상에 대한 개선이 있는지 여부를 결정하는데 또한 사용할 수 있다. 본원에서 사용된 바와 같이, "감각운동 게이팅"은 관련이 없고/없거나 침해적인 감각 자극을 걸러 내는 능력을 지칭한다. 따라서, 감각운동 게이팅 행동이 결손된 대상체는 자극을 걸러 내는 능력이 손상되었을 수 있고/있거나, 강하게 자극적인 환경에 대처하는데 어려움이 있을 수 있다. 예를 들어, 감각운동 게이팅 행동을 프리펩스 억제 (PPI) 테스트에서 평가할 수 있다. 본원에 기술된 일부 실시양태에 따라, 대상체가 개선된 감각운동 게이팅을 필요로 하는 것으로, 예를 들어, 관련이 없는 감각 자극 예컨대 배경 소음, 배경 조명 등을 걸러 내는 것의 개선을 필요로 하는 것으로 확인된다. 본원에서 사용된 바와 같이, "의사소통 행동"은 음성 및 비-음성적인 사회적 의사소통을 포함하여, 의사소통, 언어 이해 및 산출, 및 사교성을 지칭한다. 일부 실시양태에서, 손상된 사교성을 기초로 대상체가 의사소통 행동에서 결손이 있는 것으로 확인된다. 일부 실시양태에서, 손상된 언어 이해 및/또는 산출을 기초로 대상체가 의사소통 행동에서 결손이 있는 것으로 확인된다.

[0032] 본원에서 사용된 바와 같이, 용어 "행동 수행의 개선"은 ASD, 정신분열병, 또는 ASD 또는 정신분열병의 증상 중 하나 이상이 있는 병리학적인 상태를 앓고 있는 개체가 나타내는 행동 장애, 증상 및/또는 이상 중 하나 이상이, 어떠한 정도든, 중증도 또는 빈도 면에서 예방 또는 감소되는 것을 지칭한다. 행동 증상의 비제한적인 예는 손상된 의사소통, 손상된 사교성, 손상된 언어 이해 및/또는 산출, 손상된 감각운동 게이팅 행동, 반복 행동, 및 증가된 불안을 포함한다. 개선은 치료를 받는 개체 자신에 의해 또는 또 다른 사람 (의사 등)에 의해 관찰된다. 일부 실시양태에서, 본원에 기술된 바와 같은 유효량의 박테로이데스 및/또는 엔테로코쿠스 박테리아를 포함하는 프로바이오틱이 대상체에게 투여된다. 일부 실시양태에서, 프로바이오틱 투여 후 대상체에서 감각운동 게이팅 행동이 개선된다. 일부 실시양태에서, 프로바이오틱 투여 후 대상체에서 의사소통 행동이 개선된다. 개선될 수 있는 의사소통 행동의 예는 의사소통, 사교성, 및 언어 이해 및/또는 산출을 포함한다. 일부 실시양태에서, 프로바이오틱 투여 후 대상체에서 불안 행동이 개선된다. 일부 실시양태에서, 프로바이오틱 투여 후 대상체에서 반복 행동이 개선된다. 일부 실시양태에서, 프로바이오틱 투여 후 대상체에서 감각운동 게이팅 행동 및 의사소통 행동이 개선된다.

[0033] 본원에서 사용된 바와 같이, 용어 "치료"는 대상체, 특히 ASD, 정신분열병, 또는 ASD 또는 정신분열병의 증상 중 하나 이상이 있는 병리학적인 상태를 앓고 있는 대상체가 나타내는 질환, 장애 또는 생리학적 상태에 반응하여 이루어진 임상 시술을 지칭한다. 치료 목적은 증상의 경감 또는 예방, 질환, 장애 또는 상태의 진행 또는 악화를 느리게 하거나 정지시키는 것, 및 질환, 장애 또는 상태의 완화 중 하나 이상을 포함할 수 있지만, 이에 제한되지 않는다. 일부 실시양태에서, "치료"는 치료적 처치 및 예방적 또는 방지적 수단 양쪽 모두를 지칭한다. 치료를 필요로 하는 이는 질환 또는 장애 또는 바람직하지 않은 생리학적 상태에 이미 걸린 이, 뿐만 아니라 질환 또는 장애 또는 바람직하지 않은 생리학적 상태가 예방되어야 하는 이를 포함한다. 예를 들어, 일부 실시양태에서, 치료는 ASD-관련 행동 예컨대 감각운동 게이팅 행동 결손 및/또는 의사소통 행동 결손을 포함하여 대상체의 행동 수행을 개선할 수 있다. 본원에서 사용된 바와 같이, 용어 "예방"은 추후에 이러한 행동 증상을 나타내는 개체의 부담을 감소시키는 임의의 활동을 지칭한다. 이는 1차, 2차 및 3차 예방 수준으로 일어나고, 여기서 a) 1차 예방은 증상/장애/상태의 발달을 막고; b) 2차 예방 활동은 상태/장애/증상 치료의 초기 단계를 겨냥함으로써, 시술이 상태/장애/증상의 진행 및 증상의 출현을 방지할 기회를 증가시키며; c) 3차 예방은, 예를 들어, 기능을 복원시키고/시키거나 임의의 상태/장애/증상 또는 관련된 합병증을 감소시킴으로써, 이미 확립된 상태/장애/증상의 음성 영향을 감소시킨다.

[0034] "제약상 허용되는" 담체는 사용된 투여량 및 농도에서 이에 노출되는 세포 또는 포유동물에게 독성이 없는 것이다. 본원에서의 방법 및 용도 및 조성물 및 키트에 따른 "제약상 허용되는" 담체는 선택된 적용 방식 예컨대 경구 투여 또는 주사에 적절하고 통상적인 제약 제제 형태, 예컨대 고체 예컨대 정제, 과립, 분말, 캡슐, 및 액체 예컨대 용액, 에멀션, 현탁액 등으로 투여되는 유기 또는 무기, 고체 또는 액체 부형제를 포함할 수 있지만, 이에 제한되지 않는다. 종종 생리학상 허용되는 담체는 수성 pH 완충 용액 예컨대 포스페이트 완충제 또는 시트레이트 완충제이다. 생리학상 허용되는 담체는 하기 중 하나 이상을 또한 포함할 수 있다: 아스코르브산을 포함하는 항산화제, 저분자량 (잔기 약 10개 미만)의 폴리펩티드, 단백질, 예컨대 혈청 알부민, 젤라틴, 면역글로불린; 친수성 중합체 예컨대 폴리비닐피롤리돈, 아미노산, 글루코스, 만노스 또는 텍스트린을 포함하는 탄수

화물, 킬레이트제 예컨대 EDTA, 당 알콜 예컨대 만니톨 또는 소르비톨, 염-형성 카운터 이온 예컨대 나트륨, 및 비이온성 계면활성제 예컨대 트윈(TWEEN)TM 계면활성제, 폴리에틸렌 글리콜 (PEG), 및 플루로닉스(PLURONICS)TM 계면활성제. 보조제, 안정화제, 유화제, 윤활제, 결합제, pH 조정제 조절제, 등장성 작용제 및 기타 통상적인 첨가물이 담체에 또한 첨가될 수 있다.

[0035] 본원에서의 방법 및 용도 및 조성물 및 키트에 따른 제약상 허용되는 또는 적합한 담체는 위장관 손상 상황에 이로운 것으로 공지된 다른 화합물 (예를 들어, 항산화제, 예컨대 비타민 C, 비타민 E, 셀레늄 또는 아연); 또는 식품 조성물을 포함할 수 있다. 식품 조성물은 우유, 요거트, 응유, 치즈, 발효유, 우유를 기초로 하는 발효 제품, 아이스크림, 발효 곡물을 기초로 하는 제품, 우유를 기초로 하는 분말, 유아용 조제식, 정제, 액체 박테리아 현탁액, 건식 경구 보충물, 또는 습식 경구 보충물일 수 있지만, 이에 제한되지 않는다.

[0036] 본원에서 사용된 바와 같이, 용어 "프로바이오틱"은 적합한 양으로 투여되었을 때 숙주에게 건강 이점을 부여하는 살아 있는 미생물을 지칭한다. 본원에서의 방법 및 용도 및 조성물 및 키트에 따른 프로바이오틱은 식품 및 건강보조식품 (예를 들어, 캡슐, 정제, 분말 및 액체이지만, 이에 제한되지 않음)에서 이용가능하다. 프로바이오틱을 함유하는 식품의 비제한적인 예는 유제품 예컨대 요거트, 발효유, 비발효유, 스무디, 버터, 크림, 후머스, 콤파차, 샐러드 드레싱, 미소, 템페, 영양 바, 및 일부 주스 및 콩 음료를 포함한다. 일부 실시양태에서, 프로바이오틱은 단일 미생물을 포함한다. 일부 실시양태에서, 프로바이오틱은 미생물의 조합물을 포함한다. 일부 실시양태에서, 프로바이오틱은 단일 조성물을 포함한다. 일부 실시양태에서, 프로바이오틱은 함께 사용될 수 있는, 예를 들어 동시에 투여되거나 순차적으로 투여될 수 있는 2개 이상의 조성물을 포함한다. 프로바이오틱이 대상체에게 투여하는 것에서 사용하기 위한 "활성 성분" 또는 조성물 또는 조성물들로서의 역할을 할 수 있는 것이 주목된다. 즉, 방법, 용도 및/또는 조성물 또는 조성물들 (개별적으로 또는 합계로)이 대상체에서의 적어도 하나의 행동을 개선하도록 유효량의 프로바이오틱을 포함할 수 있다. 일부 실시양태에서, 프로바이오틱은 대상체에게 투여하기 위한 단독 활성 성분이다. 일부 실시양태에서, 프로바이오틱 이외의 박테리아, 항생제 및 약물이 실질적으로 없는 또는 없는 조성물 또는 방법 또는 용도에서 대상체에게 투여하기 위한 "단독 활성 성분" 프로바이오틱이 제공될 수 있다. 프로바이오틱이 "단독" 활성 성분이라도, 프로바이오틱을 포함하는 조성물 또는 조성물들은 대상체의 행동에 실질적으로 영향을 미치지 않지만 프로바이오틱의 기능 또는 이의 투여에 유용할 수 있는 추가 물질 (예컨대 완충제, 박테리아 공급 원료, 부형제, 풍미제, 및/또는 식품)을 포함할 수 있다.

[0037] 일부 실시양태에서, 프로바이오틱은 박테리아 (프로바이오틱 이외의 것) 및/또는 약물 또는 항생제가 실질적으로 없는 조성물 또는 조성물들 내에 포함된다. "실질적으로 없는" 또는 "실질적으로 부재하는"은 프로바이오틱 이외의 박테리아, 약물 및/또는 항생제가 미량으로 존재할 수 있지만, 프로바이오틱 이외의 박테리아, 약물 및/또는 항생제가 대상체에게 인지할 수 있는 효과를 미치지 않는다는 것으로 이해된다.

[0038] 본원에서 사용된 바와 같이, 프로바이오틱의 "유효량"은 대상체의 행동에서 임상적으로 유의한 변화를 달성하는데 충분한 양을 지칭한다.

[0039] 본원에서 사용된 바와 같이, 용어 "기능식품"은 건강 이점을 제공하는 식료품 (강화 식품 또는 건강보조식품으로서의 식료품)을 지칭한다. 기능식품은 제약 약물과 동일한 테스트 및 규정의 대상이 아니다.

[0040] ASD 및/또는 간질의 치료를 위한 프로바이오틱

[0041] 어떠한 이론에 의해서도 제한되지 않으면서, BTBR 마우스 모델이 ASD의 신경병리학적 및 행동 특색 양쪽 모두, 예를 들어 손상된 감각운동 게이팅, 상승된 불안, 및 손상된 사교성을 나타내는 것으로 생각된다. 어떠한 이론에 의해서도 제한되지 않으면서, CTNAP2 마우스 모델이 ASD 및 피질 형성이상 간질의 신경병리학적 및 행동 특색 양쪽 모두, 예를 들어 손상된 의사소통 행동 (예를 들어 사교성, 언어 이해 및/또는 산출, 및 의사소통), 감각운동 게이팅, 및 불안을 나타내는 것으로 생각된다. BTBR 마우스 및 CNTNAP2 자손을 인간의 공생 박테리아인 박테로이데스 프라길리스로 처치하는 것이 특정한 행동 결손을 수정하는 것이 본원에서 실연된다. 따라서, 일부 실시양태는 ASD 및/또는 간질의 증상에 대한 프로바이오틱 치료를 포함한다. 본원에 기술된 일부 실시양태에 따라, 박테로이데스 박테리아, 및 박테로이데스 박테리아 및 엔테로코쿠스 박테리아의 조합물 (ASD의 MIA 마우스 모델과 연관된 행동 증상에 영향을 미치는 것으로 나타남)이 ASD 및/또는 간질 (예를 들어 피질 형성이상 국소 간질)의 증상을 치료 또는 예방하는데 유용한 것으로 추가로 생각된다.

[0042] 일부 실시양태에서, 대상체는 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동의 개선을 필요로 한다 (이러한 행동들이 BTBR 마우스 모델의 행동과 일치한다는 것을 주지한다). 하기 중 적어도 하나를 포함하거나, 이로 이

투여되거나 또는 본질적으로 이로 이루어지는 유효량의 프로바이오틱이 대상체에게 투여하기 위해 제공된다 (또는 대상체를 치료하는데 사용하기 위한 것이다): (a) 박테로이데스 박테리아 (예를 들어, 비. 프라길리스, 비. 세타이오타오미크론 또는 비. 불가투스); (b) 박테로이데스 박테리아 (예를 들어, 비. 프라길리스, 비. 세타이오타오미크론 또는 비. 불가투스) 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스(*E. faecalis*), 이. 파에시움(*E. faecium*), 이. 히라에(*E. hirae*), 이. 아비움(*E. avium*), 이. 두란스(*E. durans*), 이. 갈리나룸(*E. gallinarum*), 또는 이. 카셀리플라부스(*E. casseliflavus*)); (c) 비. 프라길리스; (d) 비. 세타이오타오미크론; (e) 비. 불가투스; (g) 비. 프라길리스 및 비. 세타이오타오미크론; (h) 비. 프라길리스 및 비. 불가투스; (i) 비. 세타이오타오미크론 및 비. 불가투스; (j) 비. 프라길리스, 비. 세타이오타오미크론 및 비. 불가투스; (k) 비. 프라길리스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (l) 비. 세타이오타오미크론 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (m) 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (n) 비. 프라길리스 및 비. 세타이오타오미크론 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (o) 비. 프라길리스 및 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (p) 비. 세타이오타오미크론 및 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (q) 비. 프라길리스, 비. 세타이오타오미크론 및 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (r) 비. 프라길리스 및 이. 파에칼리스; (s) 비. 세타이오타오미크론 및 이. 파에칼리스; (t) 비. 불가투스 및 이. 파에칼리스; (u) 비. 프라길리스 및 비. 세타이오타오미크론 및 이. 파에칼리스; (v) 비. 프라길리스 및 비. 불가투스 및 이. 파에칼리스; (w) 비. 세타이오타오미크론 및 비. 불가투스 및 이. 파에칼리스; 또는 (x) 비. 프라길리스, 비. 세타이오타오미크론, 비. 불가투스 및 이. 파에칼리스. 박테리아 투여 후, 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동이 개선될 수 있다. 임의적으로, 대상체로부터의 샘플이 BTBR 모델과 연관된 유전자에서의 기능 상실 돌연변이, 예를 들어, DISC1에서의 기능 상실 돌연변이가 있는 것으로 확인된다. 임의적으로, DISC1에서의 기능 상실 돌연변이가 대상체가 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동 중 적어도 하나가 발달될 위험이 있거나 또는 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동 중 적어도 하나에 대한 치료를 필요로 한다는 것을 가리키는 것으로 결정된다. 임의적으로, 대상체에게 프로바이오틱의 확인된 박테리아 이외의 다른 박테리아가 투여되지 않거나 또는 다른 박테리아가 실질적으로 투여되지 않고, 따라서 대상체의 치료에서 사용하기 위한 프로바이오틱은 다른 박테리아가 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다. 임의적으로, 대상체에게 항생제가 투여되지 않거나 또는 항생제가 실질적으로 투여되지 않고, 따라서 대상체에게 투여하기 위한 프로바이오틱은 항생제가 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다. 임의적으로, 대상체에게 약물이 투여되지 않거나 또는 약물이 실질적으로 투여되지 않고, 따라서 대상체에게 투여하기 위한 프로바이오틱은 약물이 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다. 임의적으로, 대상체에게 제약상 활성인 성분이 투여되지 않거나 또는 제약상 활성인 성분이 실질적으로 투여되지 않고, 따라서 대상체에게 투여하기 위한 프로바이오틱은 제약상 활성인 성분이 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다. 임의적으로, 비. 프라길리스는 야생형 비. 프라길리스, 다당류 A가 결여된 돌연변이체 비. 프라길리스 (dPSA), 또는 야생형 비. 프라길리스 및 dPSA 비. 프라길리스의 조합물을 포함한다. 임의적으로, 비. 프라길리스는 야생형 비. 프라길리스, 다당류 A가 결여된 돌연변이체 비. 프라길리스 (dPSA), 또는 야생형 비. 프라길리스 및 dPSA 비. 프라길리스의 조합물을 포함한다. 일부 실시양태에서, 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동의 개선을 필요로 하는 대상체는 ASD가 있다. 일부 실시양태에서, 이러한 방법은 본원에 기술된 바와 같이 대상체가 ASD가 있는지 여부를 결정하는 단계를 추가로 포함한다.

[0043] 일부 실시양태에서, 대상체는 의사소통 행동 (언어 이해 및/또는 산출, 사교성, 및 의사소통을 포함함), 감각운동 게이팅, 불안, 및/또는 반복 행동의 개선을 필요로 한다 (이러한 행동들이 CNTNAP2 마우스 모델의 행동과 일치한다는 것을 주지한다). 하기 중 적어도 하나를 포함하거나, 이로 이루어지거나 또는 본질적으로 이로 이루어지는 유효량의 프로바이오틱이 대상체에게 투여하기 위해 제공된다 (또는 대상체를 치료하는데 사용하기 위한 것이다): (a) 박테로이데스 박테리아 (예를 들어, 비. 프라길리스, 비. 세타이오타오미크론 또는 비. 불가투스); (b) 박테로이데스 박테리아 (예를 들어, 비. 프라길리스, 비. 세타이오타오미크론 또는 비. 불가투스) 및

엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (c) 비. 프라길리스; (d) 비. 세타이오타오미크론; (e) 비. 불가투스; (g) 비. 프라길리스 및 비. 세타이오타오미크론; (h) 비. 프라길리스 및 비. 불가투스; (i) 비. 세타이오타오미크론 및 비. 불가투스; (j) 비. 프라길리스, 비. 세타이오타오미크론 및 비. 불가투스; (k) 비. 프라길리스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (l) 비. 세타이오타오미크론 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (m) 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (n) 비. 프라길리스 및 비. 세타이오타오미크론 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (o) 비. 프라길리스 및 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (p) 비. 세타이오타오미크론 및 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (q) 비. 프라길리스, 비. 세타이오타오미크론 및 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (r) 비. 프라길리스 및 이. 파에칼리스; (s) 비. 세타이오타오미크론 및 이. 파에칼리스; (t) 비. 불가투스 및 이. 파에칼리스; (u) 비. 프라길리스 및 비. 세타이오타오미크론 및 이. 파에칼리스; (v) 비. 프라길리스 및 비. 불가투스 및 이. 파에칼리스; (w) 비. 세타이오타오미크론 및 비. 불가투스 및 이. 파에칼리스; 또는 (x) 비. 프라길리스, 비. 세타이오타오미크론, 비. 불가투스 및 이. 파에칼리스. 박테리아 투여 후, 의사소통 행동, 손상된 감각운동 게이팅, 불안, 및/또는 반복 행동이 개선될 수 있다. 임의적으로, 대상체로부터의 샘플이 CNTNAP2 모델과 연관된 유전자에서의 기능 상실 돌연변이, 예를 들어, CNTNAP2에서의 기능 상실 돌연변이가 있는 것으로 확인된다. 임의적으로, CNTNAP2에서의 기능 상실 돌연변이가 대상체가 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동 중 적어도 하나가 발달될 위험이 있거나 또는 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동 중 적어도 하나에 대한 치료를 필요로 한다는 것을 가리키는 것으로 결정된다. 임의적으로, 대상체에게 프로바이오틱의 확인된 박테리아 이외의 다른 박테리아가 투여되지 않거나 또는 다른 박테리아가 실질적으로 투여되지 않고, 따라서 대상체의 치료에서 사용하기 위한 프로바이오틱은 다른 박테리아가 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다. 임의적으로, 대상체에게 항생제가 투여되지 않거나 또는 항생제가 실질적으로 투여되지 않고, 따라서 대상체에게 투여하기 위한 프로바이오틱은 항생제가 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다. 임의적으로, 대상체에게 약물 투여되지 않거나 또는 약물이 실질적으로 투여되지 않고, 따라서 대상체에게 투여하기 위한 프로바이오틱은 약물이 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다. 임의적으로, 대상체에게 제약상 활성인 성분이 투여되지 않거나 또는 제약상 활성인 성분이 실질적으로 투여되지 않고, 따라서 대상체에게 투여하기 위한 프로바이오틱은 제약상 활성인 성분이 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다. 임의적으로, 비. 프라길리스는 야생형 비. 프라길리스, 다당류 A가 결합된 돌연변이체 비. 프라길리스 (dPSA), 또는 야생형 비. 프라길리스 및 dPSA 비. 프라길리스의 조합물을 포함한다. 일부 실시양태에서, 개선될 (그리고 프로바이오틱 투여 후 개선되는) 의사소통 행동은 언어 이해 및/또는 산출, 사교성, 의사소통, 및 감각운동 게이팅 중 적어도 하나를 포함한다. 일부 실시양태에서, 의사소통 행동, 감각운동 게이팅, 불안, 및/또는 반복 행동의 개선을 필요로 하는 대상체는 ASD 또는 간질이 있다. 일부 실시양태에서, 의사소통 행동, 감각운동 게이팅, 불안, 및/또는 반복 행동의 개선을 필요로 하는 대상체는 ASD가 있다. 일부 실시양태에서, 의사소통 행동, 감각운동 게이팅, 불안, 및/또는 반복 행동의 개선을 필요로 하는 대상체는 간질이 있다. 일부 실시양태에서, 이러한 방법은 대상체가 ASD 또는 간질 (예를 들어, 피질 형성 이상 국소 간질)이 있는지 여부를 추가로 포함한다. 일부 실시양태에서, 이러한 방법은 대상체가 ASD가 있는지 여부를 추가로 포함한다. 일부 실시양태에서, 이러한 방법은 대상체가 간질 (예를 들어, 피질 형성 이상 국소 간질)이 있는지 여부를 추가로 포함한다.

[0044] 일부 실시양태에서, 프로바이오틱은 상기 개시된 박테리아 중 또는 박테리아 중 조합물 중 임의의 것을 포함하고, 단일 프로바이오틱 조성물에서 대상체에게 투여하기 위해 제공된다 (또는 대상체에게 투여하기 위한 것이다). 일부 실시양태에서, 프로바이오틱은 상기 언급된 박테리아 중 또는 박테리아 중 조합물 중 임의의 것을 포함하고, 2개 이상의 상이한 프로바이오틱 조성물에서 대상체에게 투여된다 (또는 대상체에게 투여하기 위한 것이다). 예를 들어, "박테리아 A 및 박테리아 B"의 프로바이오틱이 박테리아 A 및 박테리아 B를 포함하는 단일 조성물에서, 또는 박테리아 A를 포함하는 제1 조성물과 박테리아 B를 포함하는 제2 조성물에서 투여될 수

있다. 일부 실시양태에서, 제1 및 제2 조성물은 동시에 투여된다. 일부 실시양태에서, 제1 및 제2 조성물은 별개로 투여된다.

[0045] 일부 실시양태에서, 본원에 기술된 바와 같은 박테로이데스 박테리아의 조합물을 포함하는 프로바이오틱이 제1 박테로이데스 박테리아 또는 박테로이데스 박테리아 조합물을 포함하는 제1 조성물, 및 본원에 기술된 바와 같은 제2 박테로이데스 박테리아 또는 박테로이데스 박테리아 조합물을 포함하는 제2 조성물로서 제공된다. 일부 실시양태에서, 본원에 기술된 바와 같은 엔테로코쿠스 박테리아 및 박테로이데스 박테리아의 조합물을 포함하는 프로바이오틱이 엔테로코쿠스 박테리아를 포함하는 제1 조성물, 및 본원에 기술된 바와 같은 박테로이데스 박테리아 또는 박테로이데스 박테리아 조합물을 포함하는 제2 조성물로서 제공된다. 일부 실시양태에서, 엔테로코쿠스 박테리아 및 제1 박테로이데스 박테리아 (또는 박테로이데스 박테리아 조합물)가 제1 조성물에서 투여되고, 엔테로코쿠스 박테리아 및 제1 박테로이데스 박테리아 (또는 박테로이데스 박테리아 조합물)와 상이한 제2 박테로이데스 박테리아 (또는 박테로이데스 박테리아 조합물)가 제2 조성물에서 투여된다. 일부 실시양태에서, 엔테로코쿠스 박테리아 및 제1 박테로이데스 박테리아 (또는 박테로이데스 박테리아 조합물)가 제1 조성물에서 투여되고, 제1 박테로이데스 박테리아 (또는 박테로이데스 박테리아 조합물)와 상이한 제2 박테로이데스 박테리아 (또는 박테로이데스 박테리아 조합물)가 제2 조성물에서 투여된다.

[0046] 상기 기술된 실시양태 중 임의의 것에 따라, 임의적으로, 각각의 조성물, 용도 또는 방법은 프로바이오틱의 확인된 박테리아 이외의 박테리아가 없거나 또는 실질적으로 없다. 상기 실시양태 중 임의의 것에 따라, 임의적으로, 각각의 조성물은 항생제가 없거나 또는 실질적으로 없다. 상기 실시양태 중 임의의 것에 따라, 임의적으로, 각각의 조성물은 프로바이오틱 이외의 박테리아 및 항생제가 없거나 또는 실질적으로 없다.

[0047] 본원에 기술된 실시양태에 따라, 본원에 기술된 방법, 용도 및 조성물의 프로바이오틱은 임의의 적절한 투여 경로를 위한 것일 수 있다. 예를 들어, 프로바이오틱은 경구 투여, 직장 투여, 경피 투여, 비강내 투여 또는 흡입을 통해 대상체에게 투여될 수 있다. 일부 실시양태에서, 프로바이오틱은 대상체에게 경구로 투여된다.

[0048] 일부 실시양태에서, 프로바이오틱 조성물, 용도 또는 방법에서의 박테리아의 유효량은 적어도 약 10^4 콜로니 형성 단위 (cfu)를 포함하고, 예를 들어 적어도 약 10^4 , 10^5 , 10^6 , 10^7 , 10^8 , 10^9 , 10^{10} , 10^{11} , 10^{12} , 또는 10^{13} cfu (열거된 값 중 임의의 것 사이의 범위, 예를 들어 $10^4 - 10^8$ cfu, $10^4 - 10^9$ cfu, $10^4 - 10^{10}$ cfu, $10^4 - 10^{11}$ cfu, $10^4 - 10^{12}$ cfu, $10^4 - 10^{13}$ cfu, $10^5 - 10^8$ cfu, $10^5 - 10^9$ cfu, $10^5 - 10^{10}$ cfu, $10^5 - 10^{11}$ cfu, $10^5 - 10^{12}$ cfu, $10^5 - 10^{13}$ cfu, $10^6 - 10^8$ cfu, $10^6 - 10^9$ cfu, $10^6 - 10^{10}$ cfu, $10^6 - 10^{11}$ cfu, $10^6 - 10^{12}$ cfu, $10^6 - 10^{13}$ cfu, $10^7 - 10^8$ cfu, $10^7 - 10^9$ cfu, $10^7 - 10^{10}$ cfu, $10^7 - 10^{11}$ cfu, $10^7 - 10^{12}$ cfu, $10^7 - 10^{13}$ cfu, $10^8 - 10^{10}$ cfu, $10^8 - 10^{11}$ cfu, $10^8 - 10^{12}$ cfu, 또는 $10^8 - 10^{13}$ cfu를 포함함)를 포함한다. 일부 실시양태에서, 박테리아의 유효량은 대상체에게 투여하기 위한 조성물 내에 로그기 양 (37°C에서)의 박테리아를 포함한다. 일부 실시양태에서, 박테리아의 유효량은 대상체에게 투여하기 위한 조성물 내에 정지기 양 (37°C에서)의 박테리아를 포함한다.

[0049] ASD 증상 및/또는 간질 증상을 치료 및/또는 예방하는 방법

[0050] 일부 실시양태에서, ASD 및/또는 간질 증상을 치료하는 방법이 제공된다. 대상체는 감각운동 게이팅 행동, 불안 행동, 의사소통 행동 (언어 이해 및/또는 산출, 사교성, 및/또는 의사소통을 포함함), 및/또는 반복 행동의 개선을 필요로 하는 것으로 확인될 수 있다. 임의적으로, 대상체 (또는 대상체로부터의 샘플)가 DISC1 및/또는 CTNAP2 유전자에서의 기능 상실 돌연변이를 보유하는 것으로 결정될 수 있다. 임의적으로, DISC1 및/또는 CTNAP2 유전자에서의 기능 상실 돌연변이가 대상체가 감각운동 게이팅 행동, 불안 행동, 의사소통 행동, 및/또는 반복 행동의 개선을 필요로 한다는 것을 가리키는 것으로 결정될 수 있다. 본원에 기술된 바와 같은 유효량의 박테로이데스 박테리아, 또는 박테로이데스 및 엔테로코쿠스 박테리아의 조합물을 포함하거나, 본질적으로 이로 이루어지거나 또는 이로 이루어지는 프로바이오틱이 대상체에게 투여될 수 있다. 감각운동 게이팅 행동, 불안 행동, 의사소통 행동 및/또는 반복 행동이 개선될 수 있다. 일부 실시양태에서, 개선되는 의사소통 행동은 언어 이해 및/또는 산출, 사교성, 또는 의사소통 중 적어도 하나를 포함한다. 일부 실시양태에서, 이러한 방법은 대상체가 ASD가 있는지 여부를 결정하는 단계를 추가로 포함한다. 일부 실시양태에서, 이러한 방법은 대상체가 간질 (예를 들어, 피질 형성이상 국소 간질)이 있는지 여부를 결정하는 단계를 추가로 포함한다. 일부 실시양태에서, ASD 증상이 치료된다. 일부 실시양태에서, 간질 증상이 치료된다. 일부 실시양태에서, ASD

및 간질 증상이 치료된다. 일부 실시양태에서, 간질은 피질 형성이상 국소 간질을 포함한다.

[0051] 일부 실시양태에서, ASD 증상을 치료하는 방법이 제공된다. 대상체는 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동의 개선을 필요로 하는 것으로 확인될 수 있다. 이같은 행동들이 BTBR 모델과 일치한다는 것을 주지한다. 임의적으로, 대상체 (또는 대상체로부터의 샘플)가 DISC1 유전자에서의 기능 상실 돌연변이를 보유하는 것으로 결정될 수 있다. 임의적으로, DISC1 유전자유전자에서의 기능 상실 돌연변이가 대상체가 감각운동 게이팅 행동, 불안 행동, 의사소통 행동, 및/또는 반복 행동의 개선을 필요로 한다는 것을 가리키는 것으로 결정될 수 있다. 본원에 기술된 바와 같은 유효량의 박테로이데스 박테리아, 또는 박테로이데스 및 엔테로코쿠스 박테리아의 조합물을 포함하거나, 본질적으로 이로 이루어지거나 또는 이로 이루어지는 프로바이오틱이 대상체에게 투여될 수 있다. 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동이 개선될 수 있다. 일부 실시양태에서, 이러한 방법은 대상체가 ASD가 있는지 여부를 결정하는 단계를 추가로 포함한다. 일부 실시양태에서, 간질 증상이 치료된다.

[0052] 일부 실시양태에서, 간질 증상을 치료하는 방법이 제공된다. 대상체는 의사소통 행동 (언어 이해 및/또는 산출, 사교성, 및/또는 의사소통을 포함함), 감각운동 게이팅, 불안, 및/또는 반복 행동의 개선을 필요로 하는 것으로 확인될 수 있다 (이러한 행동들이 CTNAP2 모델과 일치한다는 것을 주지한다). 임의적으로, 대상체 (또는 대상체로부터의 샘플)가 CTNAP2 유전자에서의 기능 상실 돌연변이를 보유하는 것으로 결정될 수 있다. 임의적으로, CTNAP2 유전자에서의 기능 상실 돌연변이가 대상체가 의사소통 행동, 감각운동 게이팅 행동, 불안 행동, 및/또는 반복 행동의 개선을 필요로 한다는 것을 가리키는 것으로 결정될 수 있다. 본원에 기술된 바와 같은 유효량의 박테로이데스 박테리아, 또는 박테로이데스 및 엔테로코쿠스 박테리아의 조합물을 포함하거나, 본질적으로 이로 이루어지거나 또는 이로 이루어지는 프로바이오틱이 대상체에게 투여될 수 있다. 감각운동 게이팅 행동, 불안 행동, 의사소통 행동 및/또는 반복 행동이 개선될 수 있다. 일부 실시양태에서, 개선되는 의사소통 행동은 언어 이해 및/또는 산출, 사교성, 또는 의사소통 중 적어도 하나를 포함한다. 일부 실시양태에서, 간질은 피질 형성이상 국소 간질을 포함한다. 일부 실시양태에서, 이러한 방법은 대상체가 간질 (예를 들어, 피질 형성이상 국소 간질)이 있는지 여부를 결정하는 단계를 추가로 포함한다.

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[0054] 일부 실시양태에서, ASD 및/또는 간질 증상이 발달될 위험이 있는 대상체에서 이러한 증상을 예방하는 방법이 제공된다. 대상체는 손상된 감각운동 게이팅 행동, 불안 행동, 의사소통 행동 (언어 이해 및/또는 산출, 사교성, 및/또는 의사소통을 포함함), 및/또는 반복 행동이 발달될 위험이 있는 것으로 확인될 수 있다. 임의적으로, 대상체 (또는 대상체로부터의 샘플)가 DISC1 및/또는 CTNAP2 유전자에서의 기능 상실 돌연변이를 보유하는 것으로 결정될 수 있다. 임의적으로, DISC1 및/또는 CTNAP2 유전자에서의 기능 상실 돌연변이가 대상체가 손상된 감각운동 게이팅 행동, 불안 행동, 의사소통 행동, 및/또는 반복 행동이 발달될 위험이 있다는 것을 가리키는 것으로 결정될 수 있다. 본원에 기술된 바와 같은 유효량의 박테로이데스 박테리아, 또는 박테로이데스 및 엔테로코쿠스 박테리아의 조합물을 포함하거나, 본질적으로 이로 이루어지거나 또는 이로 이루어지는 프로바이오틱이 대상체에게 투여될 수 있다. 대상체에서 감각운동 게이팅 행동, 불안 행동, 의사소통 행동 및/또는 반복 행동에서의 최소화된 결손이 발달될 수 있거나 또는 인식가능한 결손이 발달되지 않을 수 있다. 일부 실시양태에서, 인식가능한 결손이 없이 발달되는 의사소통 행동은 언어 이해 및/또는 산출, 사교성, 또는 의사소통 중 적어도 하나를 포함한다. 일부 실시양태에서, ASD 증상이 치료된다. 일부 실시양태에서, 간질 증상이 치료된다. 일부 실시양태에서, ASD 및 간질 증상이 치료된다. 일부 실시양태에서, 간질은 피질 형성이상 국소 간질을 포함한다. 임의적으로, 위험이 있는 대상체는 유아 또는 아동이다.

[0055] 일부 실시양태에서, ASD 증상이 발달될 위험이 있는 대상체에서 ASD를 예방하는 방법이 제공된다. 대상체는 손상된 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동이 발달될 위험이 있는 것으로 확인될 수 있다. 이같은 행동들이 BTBR 모델과 일치한다는 것을 지지한다. 임의적으로, 대상체 (또는 대상체로부터의 샘플)가 DISC1 및/또는 CTNAP2 유전자에서의 기능 상실 돌연변이를 보유하는 것으로 결정될 수 있다. 임의적으로, DISC1 및/또는 CTNAP2 유전자에서의 기능 상실 돌연변이가 대상체가 손상된 감각운동 게이팅 행동, 불안 행동, 의사소통 행동, 및/또는 반복 행동이 발달될 위험이 있다는 것을 가리키는 것으로 결정될 수 있다. 본원에 기술된 바와 같은 유효량의 박테로이데스 박테리아, 또는 박테로이데스 및 엔테로코쿠스 박테리아의 조합물을 포함하거나, 본질적으로 이로 이루어지거나 또는 이로 이루어지는 프로바이오틱이 대상체에게 투여될 수 있다. 대상체에서 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동에서의 최소화된 결손이 발달될 수 있거나 또는 인식가능한 결손이 발달되지 않을 수 있다. 임의적으로, 위험이 있는 대상체는 유아 또는 아동이다.

[0056] 일부 실시양태에서, 간질 증상을 예방하는 방법이 제공된다. 대상체는 손상된 의사소통 행동 (언어 이해 및/또는 산출, 사교성, 및/또는 의사소통을 포함함), 감각운동 게이팅, 불안 행동, 및/또는 반복 행동이 발달될 위험이 있는 것으로 확인될 수 있다 (이러한 행동들이 CTNAP2 모델과 일치한다는 것을 지지한다). 임의적으로, 대상체 (또는 대상체로부터의 샘플)가 CTNAP2 유전자에서의 기능 상실 돌연변이를 보유하는 것으로 결정될 수 있다. 임의적으로, CTNAP2 유전자에서의 기능 상실 돌연변이가 대상체가 손상된 의사소통 행동, 감각운동 게이팅 행동, 불안 행동, 및/또는 반복 행동이 발달될 위험이 있다는 것을 가리키는 것으로 결정될 수 있다. 본원에 기술된 바와 같은 유효량의 박테로이데스 박테리아, 또는 박테로이데스 및 엔테로코쿠스 박테리아의 조합물을 포함하거나, 본질적으로 이로 이루어지거나 또는 이로 이루어지는 프로바이오틱이 대상체에게 투여될 수 있다. 대상체에서 감각운동 게이팅 행동, 불안 행동, 의사소통 행동 및/또는 반복 행동에서의 최소화된 결손이 발달될 수 있거나 또는 인식가능한 결손이 발달되지 않을 수 있다. 일부 실시양태에서, 의사소통 행동은 언어 이해 및/또는 산출, 사교성, 또는 의사소통 중 적어도 하나를 포함한다. 일부 실시양태에서, 간질은 피질 형성이상 국소 간질을 포함한다. 임의적으로, 위험이 있는 대상체는 유아 또는 아동이다.

[0057] 일부 실시양태에서, ASD 증상을 예방하는 방법이 제공된다. 대상체는 손상된 의사소통 행동 (언어 이해 및/또는 산출, 사교성, 및/또는 의사소통을 포함함), 감각운동 게이팅, 불안, 및/또는 반복 행동이 발달될 위험이 있는 것으로 확인될 수 있다 (이러한 행동들이 CTNAP2 모델과 일치한다는 것을 지지한다). 임의적으로, 대상체 (또는 대상체로부터의 샘플)가 CTNAP2 유전자에서의 기능 상실 돌연변이를 보유하는 것으로 결정될 수 있다. 임의적으로, CTNAP2 유전자에서의 기능 상실 돌연변이가 대상체가 손상된 의사소통 행동, 감각운동 게이팅 행동, 불안 행동, 및/또는 반복 행동이 발달될 위험이 있다는 것을 가리키는 것으로 결정될 수 있다. 본원에 기술된 바와 같은 유효량의 박테로이데스 박테리아, 또는 박테로이데스 및 엔테로코쿠스 박테리아의 조합물을 포함하거나, 본질적으로 이로 이루어지거나 또는 이로 이루어지는 프로바이오틱이 대상체에게 투여될 수 있다. 대상체에서 감각운동 게이팅 행동, 불안 행동, 의사소통 행동 및/또는 반복 행동에서의 최소화된 결손이 발달될 수 있거나 또는 인식가능한 결손이 발달되지 않을 수 있다. 일부 실시양태에서, 개선되는 의사소통 행동은 언어 이해 및/또는 산출, 사교성, 또는 의사소통 중 적어도 하나를 포함한다.

[0058] 일부 실시양태에서, 본원에 기술된 방법 중 임의의 것의 박테로이데스 박테리아, 또는 엔테로코쿠스 박테리아 및 박테로이데스 박테리아의 조합물을 포함하거나, 본질적으로 이로 이루어지거나 또는 이로 이루어지는 프로바이오틱은 하기로 이루어진 군으로부터 선택된다: (a) 박테로이데스 박테리아 (예를 들어, 비. 프라길리스, 비. 세타이오타오미크론 또는 비. 불가투스); (b) 박테로이데스 박테리아 (예를 들어, 비. 프라길리스, 비. 세타이오타오미크론 또는 비. 불가투스) 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (c) 비. 프라길리스; (d) 비. 세타이오타오미크론; (e) 비. 불가투스; (g) 비. 프라길리스 및 비. 세타이오타오미크론; (h) 비. 프라길리스 및 비. 불가투스; (i) 비. 세타이오타오미크론 및 비. 불가투스; (j) 비. 프라길리스, 비. 세타이오타오미크론 및 비. 불가투스; (k) 비. 프라길리스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (l) 비. 세타이오타오미크론 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (m) 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (n) 비. 프라길리스 및 비. 세타이오타오미크론 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (o) 비. 프라길리스 및 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스,

이. 갈리나룸, 또는 이. 카셀리플라부스); (p) 비. 세타이오타오미크론 및 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (q) 비. 프라길리스, 비. 세타이오타오미크론 및 비. 불가투스 및 엔테로코쿠스 박테리아 (예를 들어, 이. 파에칼리스, 이. 파에시움, 이. 히라에, 이. 아비움, 이. 두란스, 이. 갈리나룸, 또는 이. 카셀리플라부스); (r) 비. 프라길리스 및 이. 파에칼리스; (s) 비. 세타이오타오미크론 및 이. 파에칼리스; (t) 비. 불가투스 및 이. 파에칼리스; (u) 비. 프라길리스 및 비. 세타이오타오미크론 및 이. 파에칼리스; (v) 비. 프라길리스 및 비. 불가투스 및 이. 파에칼리스; (w) 비. 세타이오타오미크론 및 비. 불가투스 및 이. 파에칼리스; 또는 (x) 비. 프라길리스, 비. 세타이오타오미크론, 비. 불가투스 및 이. 파에칼리스. 임의적으로, 대상체에게 프로바이오틱의 확인된 박테리아 이외의 다른 박테리아가 투여되지 않거나 또는 다른 박테리아가 실질적으로 투여되지 않고, 따라서 대상체의 치료에서 사용하기 위한 프로바이오틱은 다른 박테리아가 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다. 임의적으로, 대상체에게 항생제가 투여되지 않거나 또는 항생제가 실질적으로 투여되지 않고, 따라서 대상체에게 투여하기 위한 프로바이오틱은 항생제가 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다. 임의적으로, 대상체에게 약물이 투여되지 않거나 또는 약물이 실질적으로 투여되지 않고, 따라서 대상체에게 투여하기 위한 프로바이오틱은 약물이 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다. 임의적으로, 대상체에게 제약상 활성인 성분이 투여되지 않거나 또는 제약상 활성인 성분이 실질적으로 투여되지 않고, 따라서 대상체에게 투여하기 위한 프로바이오틱은 제약상 활성인 성분이 없거나 또는 실질적으로 없는 조성물 또는 조성물들 내에 있다.

[0059]

상기 기술된 바와 같은 일부 실시양태에서, 방법은 대상체가 행동 개선을 필요로 한다는 것을 결정하는 단계를 추가로 포함한다. 일부 실시양태, 예를 들어 유아 및/또는 아동에 대해 지시된 용도, 방법 및/또는 조성물에서, ASD 행동의 위험이 있는 대상체는 모체 면역 활성화 및/또는 기타 위험 요인을 기초로 확인된다. 일부 실시양태에서, 대상체는 장, 체액 (예를 들어, 혈액 및 소변), 또는 이의 임의의 조합 내의 ASD-관련 대사산물 또는 대사산물의 조합물의 수준을 기초로 ASD가 있는 것으로 진단된다. 대상체 내의 대사산물의 수준을 기초로 ASD를 진단하는 방법이 미국 공개 번호 2014/0065132 (이에 의해 전문이 참조로 포함됨)에 상세하게 기술되어 있다. 일부 실시양태에서, 대상체는 언어 산출, 언어 인식, 충동 조절, 및/또는 사회화와 연관된 뇌 영역, 예를 들어 대뇌 피질, 뇌량, 브로카 영역, 및/또는 베르니케 영역의 영역에 병변 또는 발달 결손이 있는 것으로 결정된다. 일부 실시양태에서, ASD 행동, 예를 들어 결손성 의사소통, 발생, 감각운동, 불안, 및/또는 반복 행동, 또는 이들 중 2가지 이상의 조합이 표준 진단 기준, 예를 들어 정신 장애의 진단 및 통계 편람 (Diagnostic and Statistical Manual of Mental Disorders), 제4판 (DSM-4) 또는 제5판 (DSM-5)의 기준을 사용하여 확인된다. 일부 실시양태에서, 대상체에서의 ASD의 존재 또는 부재가 행동 테스트, 예를 들어, 자폐증 행동 점검표(Autism Behavior Checklist) (ABC), 자폐증 진단 인터뷰-개정판(Autism diagnostic Interview-Revised) (ADI-R), 아동기 자폐증 평정 척도(childhood autism Rating Scale) (CARS), 및/또는 언어-전 자폐증 진단 관찰 스케줄(Pre-Linguistic Autism Diagnostic Observation Schedule) (PL-ADOS) 중 적어도 하나를 사용하여 결정된다. 행동 테스트는 1) 강도 또는 초점 면에서 비정상적인, 하나 이상의 상동적이고 제한된 관심 패턴으로 몰두하는 것, 2) 특정한 비-기능성 일과 또는 의식에 대한 완고한 집착, c) 상동적이고 반복적인 운동 매너리즘 (예컨대 손 펄럭이기, 손가락 펄럭이기 등), 및/또는 d) 물건의 일부에 지속적으로 몰두하는 것의 존재 및/또는 정도를 검출하는 것을 포함할 수 있지만, 이에 제한되지 않는다. 행동 테스트에 포함될 수 있고, 테스트를 받는 대상체에서 행동 수행을 개선할 필요가 있음을 시사하는 행동의 비제한적인 예는 하기를 포함한다: a) 학습 시 시각적 구별의 빈약한 사용, 청력 상실이 의심되도록, 듣지 못하는 것으로 보이는 것, 때때로 큰 소음에 "놀람 반응"을 나타내지 않음, 때때로 고통스러운 자극 예컨대 타박상, 자상, 및 주사가 반응을 유발하지 않음, 밝은 빛이 눈을 향할 때 종종 깜박이지 않음, 많은 소리에 귀를 감쌌, 자연광이 존재할 때 눈을 가늘게 뜨거나 찌푸리거나 감쌌, 빈번하게 "새로운" 사람에 대한 시각적 반응이 없음, 장기간 동안 공간을 응시함을 포함하는, 감각 행동; b) 관계 행동: 빈번하게 사회적/환경적 자극에 주의를 기울이지 않음, 사회적 웃음이 없음, 손을 내밀었을 때 손을 뺀지 않음, 다른 사람의 표정/감정에 대해 비-반응성임, 시선 맞춤을 적극적으로 피함, 만져지거나 잡히는 것을 거부함, 팔이 잡혔을 때 흐느적거림, 뻣뻣하고 안기가 어려움, 놀 때 다른 아동을 모방하지 않음, 어떠한 우정도 발달시키지 않음, 종종 겁을 먹거나 매우 불안해함, 사람을 "못 본 척함"; c) 신체 및 물건 사용 행동: 장기간 동안 빙빙 돌기, 장난감을 적절하게 사용하지 않음, 특정 물건을 자신과 함께 둘 것을 고집함, 장기간 동안 스스로를 앞뒤로 흔들, 많이 달려들고 돌진함, 손을 펄럭임, 발가락으로 걸음, 머리를 부딪히고 손을 물어뜯음으로써 자해함, 물건을 많이 휘두르고 돌리고 두드림, 주위환경의 물건을 만져보고/만져보거나 냄새를 맡고/맡거나 맛봄, 복잡한 "의식" 예컨대 물건들을 줄지어 놓는 것에 몰두함, 매우 파괴적임; 및 d) 언어 행동: 한번에 주어진 간단한 명령을 따르지 않음, 대명사를 전도시킴, 어조가 없음, 다른 2명

사이에서 볼릴 때 자신의 이름에 반응하지 않음, "예" 또는 "나"를 거의 말하지 않음, 전치사를 수반하는 간단한 명령을 따르지 않음, 원하는 대상을 몸짓으로 얻음, 문구를 계속해서 반복함, 5개를 초과하는 명명된 물건을 지적할 수 없음, 하루에 0-5개의 자연스러운 단어를 사용하여 원하는 것 및 필요한 것을 의사소통함, 소리 또는 단어를 계속해서 반복함, 다른 사람의 질문 또는 서술을 되풀이함, 매일 적어도 15개지만 30개 미만인 자연스러운 문구를 사용하여 의사소통함, 간단한 작업을 배우지만 빠르게 "잊음", 일과/주위환경의 변화에 대한 강한 반응, 한 발달 영역에서 "특수한 능력"이 있고, 이는 정신 지체를 배제하는 것으로 보임, 심한 짜증 및/또는 빈번한 사소한 짜증, 물고/물거나 때리고/때리거나 발로 차는 것에 의해 다른 사람을 다치게 함, 요구가 충족될 때까지 기다리지 않음, 용변이 어려움, 빈번한 도움 없이 스스로 옷을 입지 않음, 빈번하게 주변을 의식하지 않음, 위험한 상황을 망각할 수 있음, 무생물을 조작하고 이에 열중하는 것을 선호함, 및/또는 30개월령 이전에 확인되는 발달 지연. 관련 기술 분야의 통상의 기술자는 주치의가 본원에 개시된 치료를 필요로 하는 대상체를 확인하는 방법을 알 것임을 이해할 것이다.

[0060] 상기 기술된 바와 같은 일부 실시양태에서, 방법은 유효량의 프로바이오틱을 하나 이상의 조성물의 단일 투여로 투여하는 것을 포함한다. 상기 기술된 바와 같은 일부 실시양태에서, 방법은 유효량의 프로바이오틱을 본원에 기술된 바와 같은 단일 조성물의 2회 이상의 투여에 걸쳐 투여하는 것을 포함한다. 예를 들어, 조성물들은 약 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55분, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23시간, 1, 2, 3, 4, 5, 6, 7, 8, 9 또는 10일 (열거된 값 중 임의의 2개 사이의 범위, 예를 들어 1분 - 10분, 1분 내지 30분, 1분 내지 1시간, 1분 - 2시간, 1분 - 4시간, 1분 - 12시간, 1분 - 18시간, 1분 - 1일, 10분 내지 30분, 10분 내지 1시간, 10분 - 2시간, 10분 - 4시간, 10분 - 12시간, 10분 - 18시간, 10분 - 1일, 30분 내지 1시간, 30분 - 2시간, 30분 - 4시간, 30분 - 12시간, 30분 - 18시간, 30분 - 1일, 30분 - 2일, 1시간 - 2시간, 1시간 - 4시간, 1시간 - 12시간, 1시간 - 18시간, 1시간 - 1일, 4시간 - 12시간, 4시간 - 18시간, 4시간 - 1일, 1일 - 2일, 1일 - 3일, 1일 - 4일, 1일 - 5일, 1일 - 7일, 1일 - 10일, 2일 - 3일, 2일 - 4일, 2일 - 5일, 2일 - 7일, 2일 - 10일, 또는 5일 내지 10일을 포함함) 간격으로 투여될 수 있다. 상기 기술된 바와 같은 일부 실시양태에서, 방법은 유효량의 2개 이상의 상이한 본원에 기술된 바와 같은 조성물을 단일 조성물의 2회 이상의 투여에 걸쳐 투여하는 것을 포함한다. 예를 들어, 제1 조성물의 약 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55분, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23시간, 1, 2, 3, 4, 5, 6, 7, 8, 9 또는 10일 (열거된 값 중 임의의 2개 사이의 범위, 예를 들어 1분 - 10분, 1분 내지 30분, 1분 내지 1시간, 1분 - 2시간, 1분 - 4시간, 1분 - 12시간, 1분 - 18시간, 1분 - 1일, 10분 내지 30분, 10분 내지 1시간, 10분 - 2시간, 10분 - 4시간, 10분 - 12시간, 10분 - 18시간, 10분 - 1일, 30분 내지 1시간, 30분 - 2시간, 30분 - 4시간, 30분 - 12시간, 30분 - 18시간, 30분 - 1일, 30분 - 2일, 1시간 - 2시간, 1시간 - 4시간, 1시간 - 12시간, 1시간 - 18시간, 1시간 - 1일, 4시간 - 12시간, 4시간 - 18시간, 4시간 - 1일, 1일 - 2일, 1일 - 3일, 1일 - 4일, 1일 - 5일, 1일 - 7일, 1일 - 10일, 2일 - 3일, 2일 - 4일, 2일 - 5일, 2일 - 7일, 2일 - 10일, 또는 5일 내지 10일을 포함함) 후에 제2 조성물이 투여될 수 있다. 일부 실시양태에서, 프로바이오틱은 상기 기술된 기간 중 임의의 것 동안 저속 방출 제형 (예를 들어 저속 방출 캡슐 또는 이식물)으로 투여된다.

[0061] 일부 실시양태에서, 행동 수행의 개선이 관찰될 때까지 프로바이오틱이 대상체에게 투여된다. 임의적으로, 예를 들어, 개선된 행동 수행을 고착시키거나 유지시키기 위해, 행동 수행의 개선이 관찰된 후에 프로바이오틱이 대상체에게 투여된다.

[0062] 실시예

[0063] 상기 논의된 실시양태들의 일부 측면이 하기 실시예에서 더욱 상세하게 개시되고, 이는 어떠한 방식으로든 본 개시내용의 범주를 제한하는 것으로 의도되지 않는다.

[0064] 실시예 1: 비. 프라길리스에 의한 BTBR 마우스에서의 ASD-관련 행동의 수정

[0065] 성체 BTBR 마우스에게 비. 프라길리스를 함유하는 사과 소스 또는 사과 소스 단독을 이유기 후에 1주일 동안 제공하였다. 마우스 1마리를 개방 공간에 놓고, 처음 10분 동안의 중앙 구역 내로의 진입 횟수를 기록하였다 (**도 1a**). 공간의 중앙 내에서의 기간에 대해 유사한 발견이 이루어졌다 (제시되지 않음). 총 이동 거리에 대해 큰 차이가 발견되지 않았다. 비. 프라길리스로의 처치가 이러한 이상을 예방하거나 치료한다. * $p < 0.05$; n= 실험당 30-35마리의 동물, 2회 반복.

[0066] 다수의 구슬이 깔개 위에 배열된 우리에 놓였을 때, 대조군 BTBR 수컷 마우스는 강박적으로 이를 묻는 반면,

비. 프라길리스로 처치된 BTBR 마우스는 이러한 반복/상동적 행동이 감소된다 (도 1b).

[0067] BTBR 마우스에서 배경값의 5 및 15 db 초과에서 측정된 바와 같은 프리펄스 억제 (PPI)가 관찰되었다 (도 1c). 비. 프라길리스로의 처치가 감각운동 게이팅의 이러한 척도를 정상화하였다. * $p < 0.05$ ** $p < 0.01$. n= 실험 당 15-20마리의 동물.

[0068] 따라서, 본원에서의 일부 실시양태에 따라 BTBR 자폐증 모델 성체 마우스를 박테로이데스 박테리아로 처치하는 것이 ASD와 연관된 행동 결손을 개선한다.

[0069] 실시예 2: 비. 프라길리스에 의한 CNTNAP2 마우스에서의 ASD-관련 행동의 수정

[0070] 야생형 마우스 (C57BU6), 이종접합형 (Her) 마우스 (CNTNAP2+/-) 및 녹아웃 (KO) (CNTNAP2-/-) 마우스를 다양한 ASD-연관 행동에 대해 테스트하였다. 사과 소스 단독을 이유기 후에 3주 동안 제공한 성체 대조군 및 비. 프라길리스를 함유하는 사과 소스를 이유기 후에 3주 동안 제공한 성체 마우스를 테스트하였다. 문헌 [Penagarikano et al. (2011)]에 보고된 바와 같이, 돌연변이체 마우스는 과다활동성이다. 개방 공간에서의 과다활동을 측정하였다 (도 1d 및 1e). 현저하게, 이동 거리 (도 1d) 및 평균 속도 (도 1e)에 의해 측정되는 바와 같이, 사과 소스 내의 비. 프라길리스 급식이 과다활동을 예방할 수 있었다. 유사하게, CNTNAP2-/-는 문헌 [Penagarikano et al. (2011)]에 평가된 바와 같이 반복 행동을 나타내고, 이는 자가-털손질에 의해 측정될 수 있다. 자가-털손질의 측정 시 (도 1f), 비. 프라길리스 처치가 이러한 ASD-유사 자가-털손질 행동을 호전시킨다. * $p < 0.05$; NS=유의하지 않음. N=4-11마리의 마우스, 2회 반복.

[0071] 따라서, 본원에서의 일부 실시양태에 따라 CNTNAP2 자폐증 모델 성체 마우스를 박테로이데스 박테리아로 처치하는 것이 ASD와 연관된 행동 결손을 개선한다.

[0072] 실시예 3: 비. 프라길리스에 의한 ASD-관련 행동의 수정

[0073] 성인 대상체가 감각운동 게이팅 행동, 불안 행동, 및 사교성 행동의 조합이 있는 것으로 확인된다. 대상체가 본질적으로 비. 프라길리스로 이루어지는 유효량의 프로바이오틱을 포함하는 시리얼 바를 3주 동안 매주 섭취한다. 약 3주의 시리얼 바 섭취 후, 대상체가 청각 자극에 대한 증가된 반응, 감소된 불안, 및 더욱 빈번한 사회적 상호작용을 나타낼 것으로 예상된다.

[0074] 실시예 4: 박테로이데스에 의한 ASD-관련 행동의 예방

[0075] 인간 아동 대상체가 DISC1 유전자에서의 기능 상실 돌연변이에 대해 이형접합성인 것으로 결정되고, 따라서 손상된 의사소통 행동 (언어 이해 및/또는 산출, 사교성, 의사소통), 손상된 감각운동 게이팅, 불안, 및 반복 행동을 포함하는 ASD 행동의 위험이 있는 것으로 결정된다. 대상체가 본질적으로 비. 세타이오타오미크론으로 이루어지는 유효량의 프로바이오틱을 포함하는 요거트 음료를 6개월 동안 4일마다 1번 음용한다. 대상체에서 의사소통 행동, 감각운동 게이팅 행동, 불안, 및 반복 행동에서의 최소의 손상이 발달될 것으로 예상된다.

[0076] 실시예 5: 비. 프라길리스 및 이. 파에칼리스에 의한 간질-관련 행동의 수정

[0077] 사춘기의 인간 대상체가 손상된 감각운동 게이팅, 손상된 언어 이해 및 산출, 및 피질 형성이상 국소 간질에 특징적인 간질 발작이 있는 것으로 확인된다. 대상체가 간질 치료를 필요로 하는 것으로 결정된다. 대상체는 본질적으로 비. 프라길리스 및 이. 파에칼리스로 이루어지는 프로바이오틱을 포함하는 젤 캡슐을 증상이 개선될 것으로 예상될 때까지 매일 섭취한다.

[0078] 앞서 기술된 실시양태 중 적어도 일부에서, 교체가 기술적으로 실행이 불가능하지 않는 한, 실시양태에 사용된 하나 이상의 요소가 또 다른 실시양태에서 상호교환가능하게 사용될 수 있다. 관련 분야의 통상의 기술자는 청구된 주제의 범주를 벗어나지 않으면서 상기 기술된 방법 및 구조에 다양한 다른 생략, 부가 및 변형이 이루어질 수 있다는 것을 이해할 것이다. 모든 이같은 변형 및 변화는 첨부된 청구항에 의해 정의되는 바와 같은 이러한 주제의 범주 내에 속하는 것으로 의도된다.

[0079] 본원에서의 실질적으로 임의의 복수형 및/또는 단수형 용어의 사용과 관련하여, 관련 기술 분야의 통상의 기술자는 문맥 및/또는 용도에 적합한 바와 같이 복수형으로부터 단수형으로 및/또는 단수형으로부터 복수형으로 바꿀 수 있다. 다양한 단수형/복수형 변환이 명료성을 위해 본원에서 명확하게 제시될 수 있다.

[0080] 관련 분야의 통상의 기술자는, 일반적으로, 본원에서, 특히 첨부된 청구항 (예를 들어, 첨부된 청구항의 본문)에서 사용된 용어가 일반적으로 "개방형" 용어로서 의도된다는 것을 이해할 것이다 (예를 들어, 용어 "~"를 포함하는 "은" "~"를 포함하지만 이에 제한되지 않는"으로 해석되어야 하고, 용어 "~"를 갖는"은 "적어도 ~"를 갖는"으로

해석되어야 하며, 용어 "~를 포함한다"는 "~를 포함하지만, 이에 제한되지 않는다"로 해석되어야 하는 식이다). 관련 분야의 통상의 기술자는 도입된 청구항 기재의 특정 개수가 의도되는 경우, 이같은 의도가 청구항에 명시적으로 기재될 것이고, 이같은 기재의 부재 시에는 이같은 의도가 존재하지 않는다는 것을 추가로 이해할 것이다. 예를 들어, 이해를 돕기 위해, 하기의 첨부된 청구항은 청구항 기재를 도입하기 위해 도입구 "적어도 하나" 및 "하나 이상"을 사용하는 것을 함유할 수 있다. 그러나, 이같은 구의 사용은 부정관사 "a" 또는 "an"에 의한 청구항 기재의 도입이 이같은 도입된 청구항 기재를 함유하는 임의의 특정한 청구항을, 동일한 청구항이 도입구 "하나 이상" 또는 "적어도 하나" 및 부정관사 예컨대 "a" 또는 "an"을 포함하는 경우에도, 오직 1개의 이같은 기재를 함유하는 실시양태로 제한하는 것을 의미하는 것으로 해석되지 않아야 한다 (예를 들어, "a" 및/또는 "an"은 "적어도 하나" 또는 "하나 이상"을 의미하는 것으로 해석되어야 한다); 이는 청구항 기재를 도입하기 위해 사용된 정관사의 사용에 대해서도 마찬가지이다. 추가적으로, 도입된 청구항 기재의 특정 개수가 명시적으로 기재되더라도, 관련 분야의 통상의 기술자는 이같은 기재가 적어도 기재된 개수를 의미하는 것으로 해석되어야 한다는 것을 인지할 것이다 (예를 들어, 다른 수식구 없이 "2개의 기재"로만 기재하는 것은 적어도 2개의 기재 또는 2개 이상의 기재를 의미한다). 또한, "A, B, 및 C 등 중 적어도 하나"와 유사한 관례가 사용되는 경우에, 일반적으로 이같은 구문은 관련 분야의 통상의 기술자가 이러한 관례를 이해할 것이라는 의미에서 의도된다 (예를 들어, "A, B, 및 C 중 적어도 하나를 갖는 시스템"은 A를 단독으로, B를 단독으로, C를 단독으로, A 및 B를 함께, A 및 C를 함께, B 및 C를 함께, 및/또는 A, B 및 C를 함께 갖는 식의 시스템을 포함하지만, 이에 제한되지 않을 것이다). "A, B, 또는 C 등 중 적어도 하나"와 유사한 관례가 사용되는 경우에, 일반적으로 이같은 구문은 관련 분야의 통상의 기술자가 이러한 관례를 이해할 것이라는 의미에서 의도된다 (예를 들어, "A, B, 또는 C 중 적어도 하나를 갖는 시스템"은 A를 단독으로, B를 단독으로, C를 단독으로, A 및 B를 함께, A 및 C를 함께, B 및 C를 함께, 및/또는 A, B 및 C를 함께 갖는 식의 시스템을 포함하지만, 이에 제한되지 않을 것이다). 관련 분야의 통상의 기술자는 2개 이상의 대안적인 용어를 나타내는 사실상 임의의 이접적 단어 및/또는 문구가, 상세한 설명에서든, 청구항에서든 또는 도면에서든, 용어 중 하나, 용어 중 어느 하나, 또는 양쪽 모두의 용어를 포함할 가능성을 고려하는 것으로 이해되어야 한다는 것을 추가로 이해할 것이다. 예를 들어, 문구 "A 또는 B"는 "A" 또는 "B" 또는 "A 및 B"의 가능성을 포함하는 것으로 이해될 것이다.

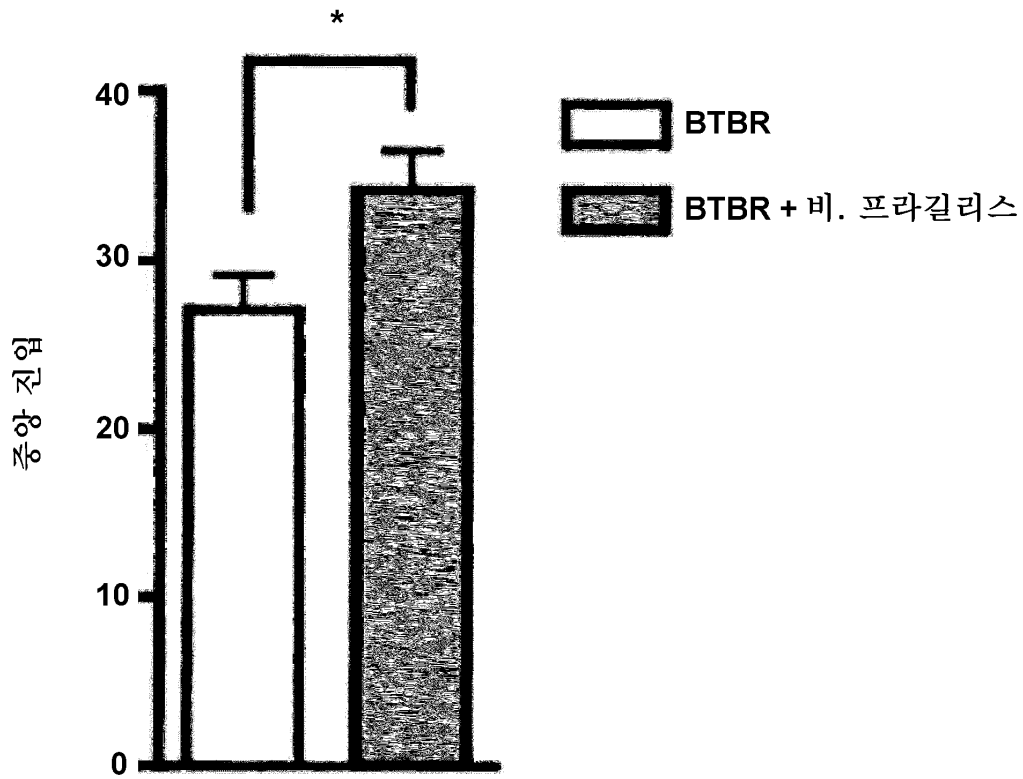
[0081] 또한, 본 개시내용의 특색 또는 측면이 마쿠쉬 그룹의 식으로 기술되는 경우, 관련 분야의 통상의 기술자는 본 개시내용이 이에 의해 마쿠쉬 그룹의 임의의 개별적인 구성원 또는 구성원들의 하위그룹의 식으로 또한 기술된다는 것을 인지할 것이다.

[0082] 관련 분야의 통상의 기술자가 이해할 바와 같이, 임의의 모든 목적을 위해, 예컨대 서면 설명을 제공하는 측면에서, 본원에 개시된 모든 범위는 임의의 모든 가능한 하위 범위 및 이의 하위 범위의 조합을 또한 포함한다. 임의의 열거된 범위는 동일한 범위가 적어도 동등한 절반, 1/3, 1/4, 1/5, 1/10 등으로 분할되는 것을 충분히 기술하고 가능하게 한다는 것이 쉽게 인식될 수 있다. 비제한적인 예로서, 본원에 논의된 각각의 범위는 하위 1/3, 중간 1/3 및 상위 1/3 등으로 용이하게 분할될 수 있다. 관련 분야의 통상의 기술자가 또한 이해할 바와 같이, 모든 언어 예컨대 "~ 이하", "적어도", "~ 초과", "~ 미만" 등은 기재된 숫자를 포함하고, 상기 논의된 바와 같이 후속적으로 하위 범위로 분할될 수 있는 범위를 지칭한다. 마지막으로, 관련 분야의 통상의 기술자가 이해할 바와 같이, 범위는 각각의 개별적인 구성원을 포함한다. 따라서, 예를 들어, 1-3개의 항목이 있는 군은 1, 2 또는 3개의 항목이 있는 군을 지칭한다. 유사하게, 1-5개의 항목이 있는 군은 1, 2, 3, 4, 또는 5개의 항목이 있는 군을 포함하는 식이다.

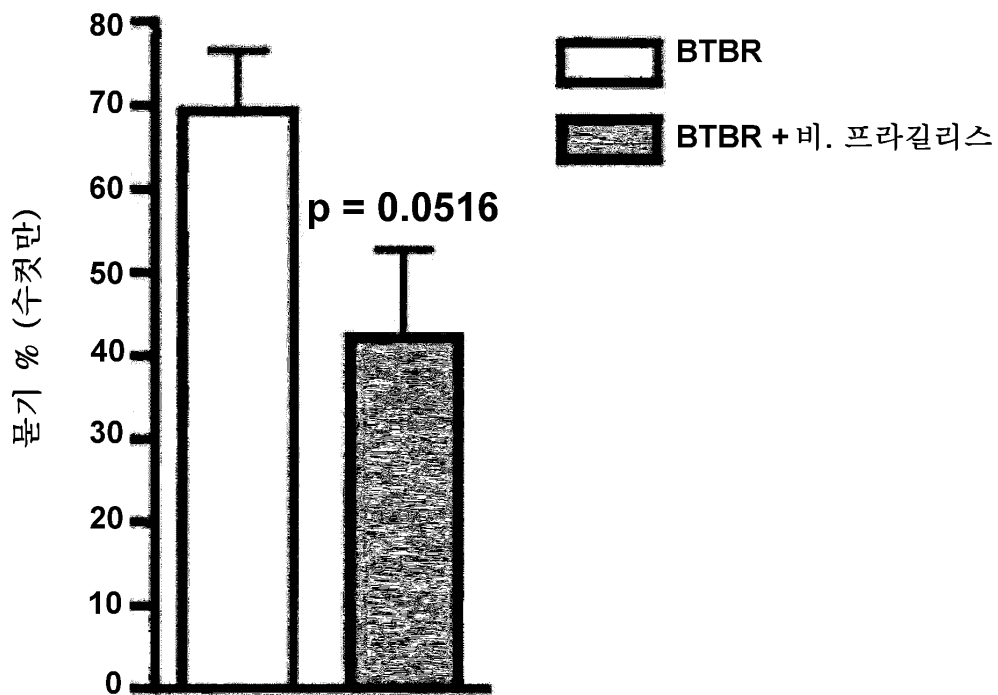
[0083] 다양한 측면 및 실시양태가 본원에서 개시되었지만, 다른 측면 및 실시양태가 관련 분야의 통상의 기술자에게 명백할 것이다. 본원에 개시된 다양한 측면 및 실시양태는 설명을 목적으로 하고 제한적인 것으로 의도되지 않으며, 진정한 범주 및 취지는 하기의 청구항에 의해 지시된다.

도면

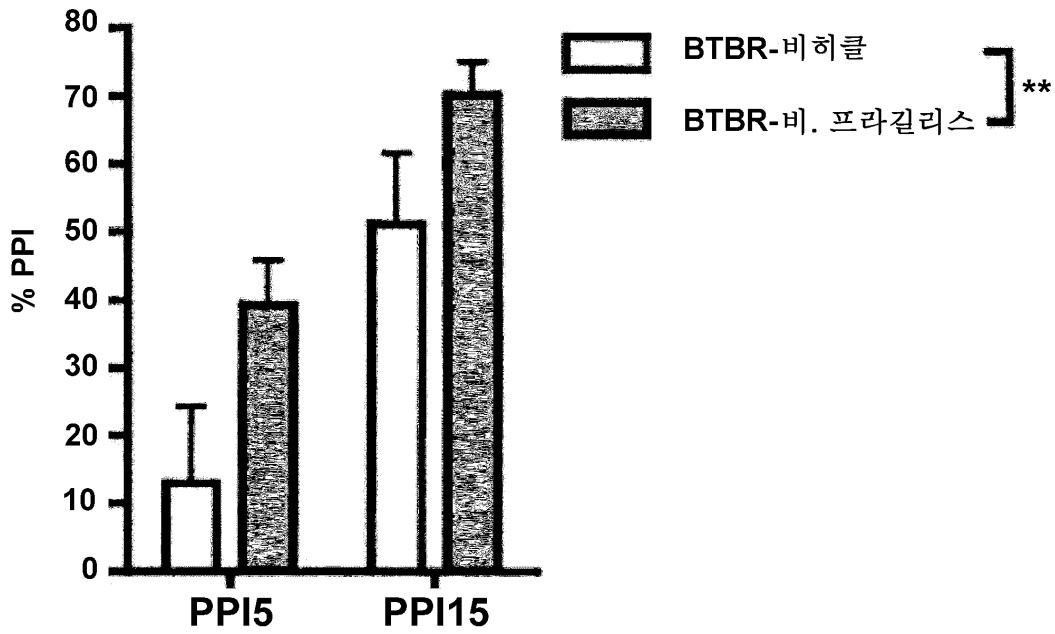
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도면1b

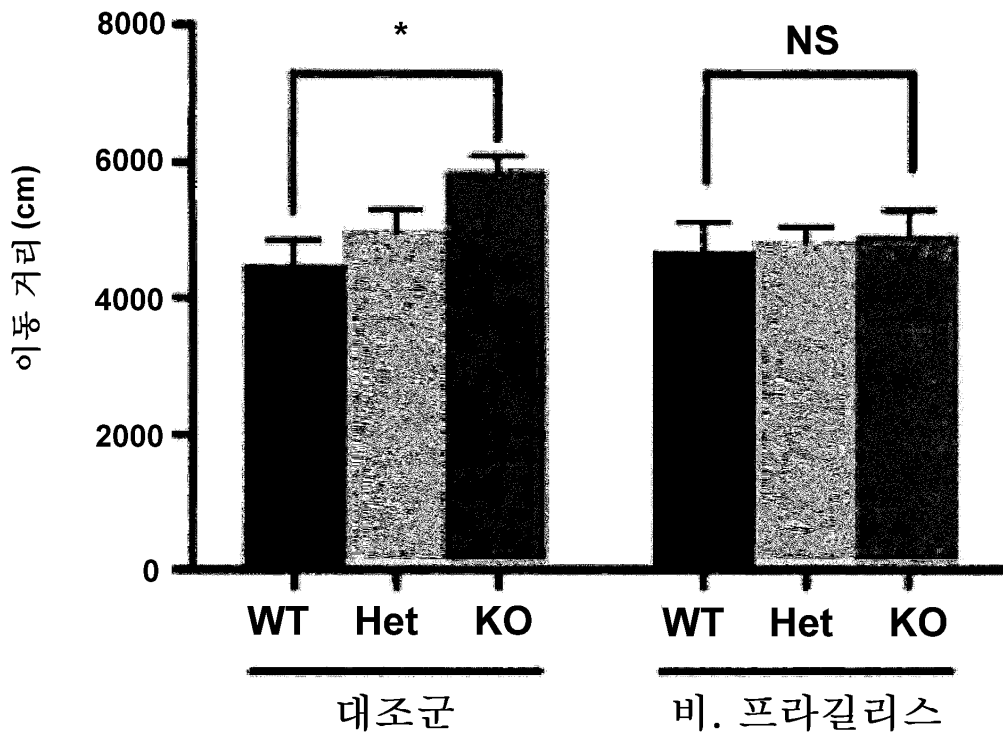


도면1c

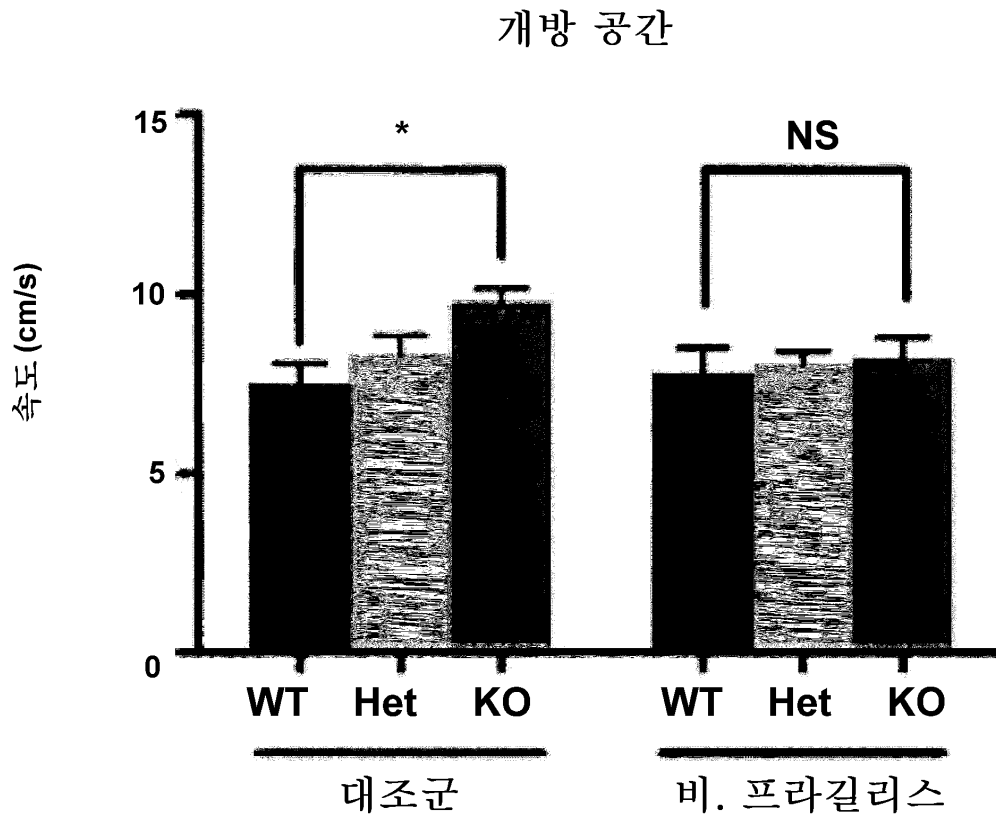


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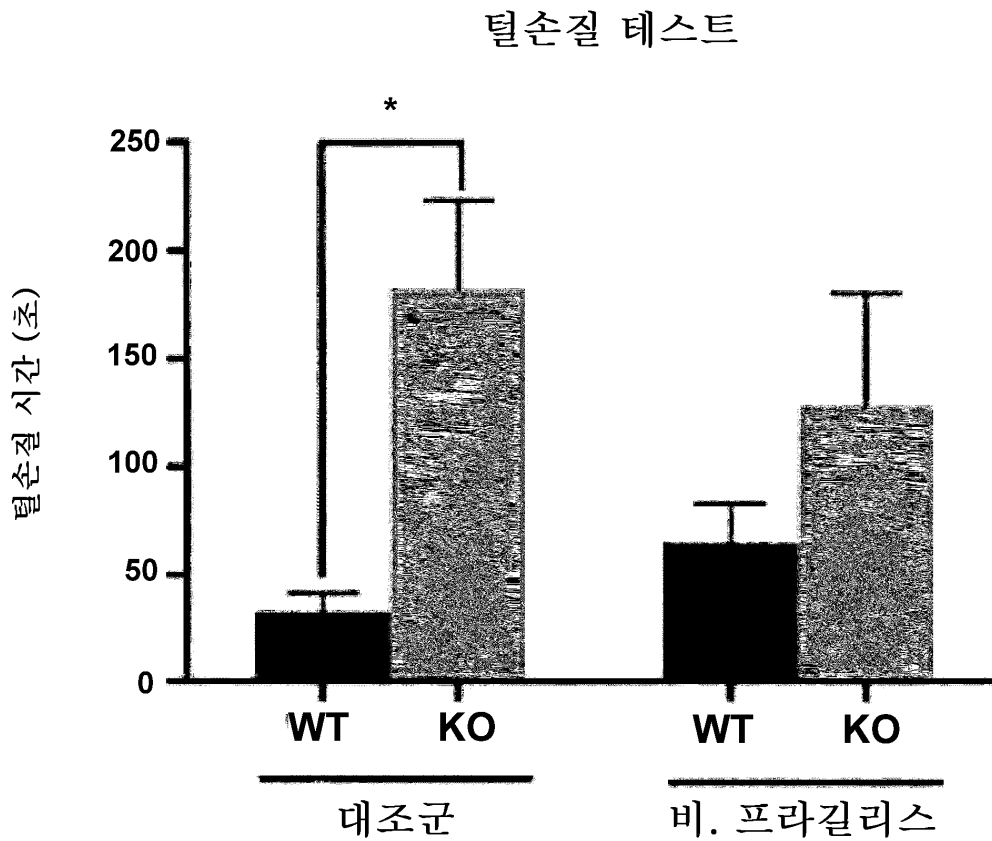
개방 공간



도면1e



도면1f



서열 목록

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