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(54)名稱

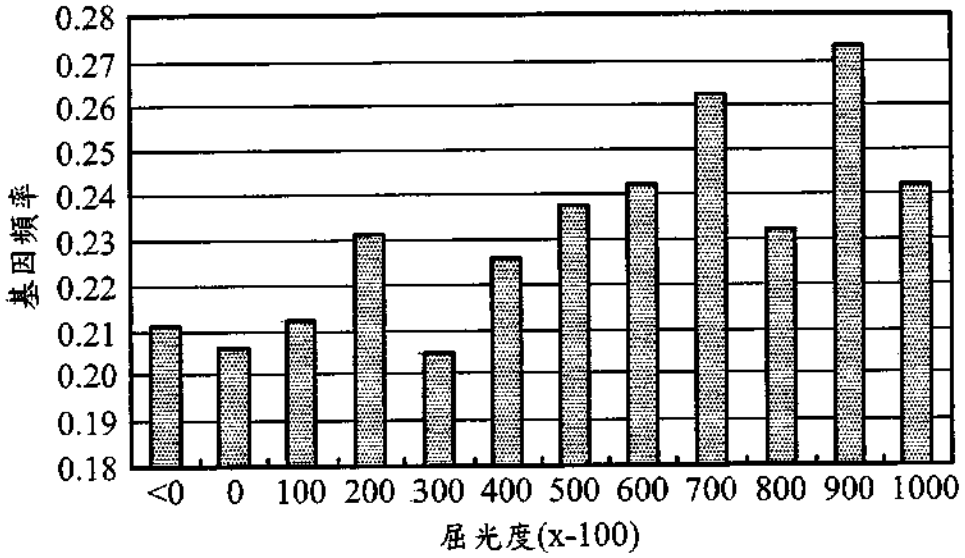
決定個體罹患高度近視的風險性之方法

METHOD OF DETERMINING SUSCEPTIBILITY OF HIGH MYOPIA

(57)摘要

本發明係提供一種利用 BICD1 基因來檢測近視及/或近視相關併發症的方法。本發明之方法包括由一個體中獲得一生物樣本，檢測此生物樣本中 BICD1 基因之至少一種 SNP 基因型，其中此 SNP 基因型的存在顯示該個體具近視感受性。此 SNP 基因型係擇自下到所組成之族群：SNPs rs7966276、rs1151029、rs2650122 及 rs10771923。此外，本發明更提供一種篩選治療或抑制近視物質的方法，以及一種評估一個體對於近視治療藥物反應的方法。

Using the BICD1 gene as a marker for diagnosing myopia and/or myopia related complications is provided. The method includes obtaining a biological sample from a subject, and determining at least one SNP genotype in the BICD1 gene in the biological sample, wherein the presence of the SNP genotype indicates that the subject is susceptible to myopia. The SNP genotype is selected from the group consisting of SNPs rs7966276, rs1151029, rs2650122, and rs10771923. In addition, the present invention also provides a method of screening a material for preventing, treating myopia, and a method of assessing a subject for probability of response to a myopia therapeutic agent.


0.28
0.27
0.26
0.25
0.24
0.23
0.22
0.21
0.20
0.19
0.18
基因頻率
<0
0
100
200
300
400
500
600
700
800
900
1000
屈光度(x-100)

第 1 圖

附件5.34

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公告本

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一、發明名稱：（中文/英文）

決定個體罹患高度近視的風險性之方法

Method of determining susceptibility of high myopia

二、中文發明摘要：

本發明係提供一種利用 BICD1 基因來檢測近視及/或近視相關併發症的方法。本發明之方法包括由一個體中獲得一生物樣本，檢測此生物樣本中 BICD1 基因之至少一種 SNP 基因型，其中此 SNP 基因型的存在顯示該個體具近視感受性。此 SNP 基因型係擇自下到所組成之族群：SNPs rs7966276、rs1151029、rs2650122 及 rs10771923。此外，本發明更提供一種篩選治療或抑制近視物質的方法，以及一種評估一個體對於近視治療藥物反應的方法。

三、英文發明摘要：

Using the BICD1 gene as a marker for diagnosing myopia and/or myopia related complications is provided. The method includes obtaining a biological sample from a subject, and determining at least one SNP genotype in the BICD1 gene in the biological sample, wherein the presence of the SNP genotype indicates that the subject is susceptible to myopia. The SNP genotype is selected from the group consisting of SNPs rs7966276, rs1151029, rs2650122, and

rs10771923. In addition, the present invention also provides a method of screening a material for preventing, treating myopia, and a method of assessing a subject for probability of response to a myopia therapeutic agent.

四、指定代表圖：

(一)本案指定代表圖為：第 1 圖。

(二)本代表圖之元件符號簡單說明：無。

五、本案若有化學式時，請揭示最能顯示發明特徵的化學式：

無。

六、發明說明：

【發明所屬之技術領域】

本發明係有關於一種檢測近視的方法，且特別有關於一種利用檢測 BICD1 基因之單核苷酸多型性(SNP, single nucleotide polymorphism)來檢測近視及/或近視相關併發症的方法。此外，本發明更有關於一種篩選治療或抑制近視物質的方法。

【先前技術】

近視係指在放鬆的情況下，平行於視軸的平行光線通過眼球屈光系統的折射彙聚在視網膜前，屬於一種屈光不正。近視的人在看遠處的物體時，不能在視網膜上清晰的成像，使得影像聚焦於眼球的玻璃體中，而非視網膜上。

近視廣泛地存在於世界上，近視的治療與族群、性別及年記有關(Invest Ophthalmol Vis Sci 1997;38:334-40；Optom Vis Sci 2001;78:234-9；J Formos Med Assoc 2001;100:684-91)。在美國，12至54歲的國民有25%的人罹患近視(Arch Ophthalmol 1983;101:405-7)，且白人罹患近視的比率(28.1%)高於非裔族群(19.4%)(Invest Ophthalmol Vis Sci 1997;38:334-40)。在所有的近視族群中，高度近視(屈光度≤ -5.0 D)的比例可達27%至33%，盛行率為1.7%至2%(Arch Ophthalmol 1983;101:405-7)。在世界上，台灣是屬於近視的高危險地區。若以屈光度≤ -6.0 D來作為高度近視，台灣的高度近視比例高於亞洲各國，且在台灣有18%的男性學童及24%的女性學童罹患近視(J Formos Med Assoc 2001;100:684-91)，此比例甚至高

於新加坡年輕人的近比例(13.1%)(Optom Vis Sci 2001;78:234-9)，在1995及2000年的全國調查中發現台灣的近視盛行率仍持續增加。

高度近視可能會導致失明，例如，其與視網膜剝離、黃斑點退化及青光眼有關。在美國所有的失明學童中有5.6%與近視有關。雖然，近視可以藉由眼鏡、隱形眼鏡、角膜矯正術及雷射屈光矯正手術(LASIK)治療或校正，但上述方法皆無法抑制因近視併發症所造成視網膜剝離、黃斑點退化及青光眼的產生。此外，過度使用隱形眼鏡(Curr Opin Ophthalmol 1998;9:66-71)、角膜矯正術(J Refract Surg 2003;19:S247-9)及其他外科手術也可能會增加眼睛產生併發症的風險。在美國，每年必須花費2億5千萬在治療近視上(Arch Ophthalmol 1994;112:1526-30)。

目前已證實許多環境因子與近視有關，由雙胞胎研究顯示近視與遺傳有顯著的關係，家族遺傳率估計在58%至90%之間 (Invest Ophthalmol Vis Sci 2001;42:1232-6；Genet Epidemiol 1988;5:171-81；Hum Hered 1991;41:151-6；Br J Ophthalmol 2001;85:1470-6)。實驗證實家族病史是高度近視的重要原因(Invest Ophthalmol Vis Sci 2004;45:3446-52； Optom Vis Sci 1996;73:279-82；JAMA 1994;271:1323-7； Invest Ophthalmol Vis Sci 2002;43:3633-40；Optom Vis Sci 1999;76:387-92；Invest Ophthalmol Vis Sci 2004;45:2873-8)。然而，只有少許的研究發現與近視相關的基因，但都無法得到大型資料的證實。

因此，醫學上亟需要一種生物標的來作為檢測、治療

及減緩近視及其併發症的參考。

【發明內容】

本發明係提供一種決定一個體是否對近視具有感受性的方法，包括：由該個體中獲得一生物樣本，以及測定該生物樣本中的BICD1基因(序列識別號1)之至少一單核苷酸多型性(SNP)，其中該單核苷酸多型性的危險基因型存在，則表示該個體對近視具有感受性。

本發明另提供一種篩選抑制或治療近視及/或近視相關併發症物質的方法，包括使一測試物質及一表現BICD1基因之細胞相互接觸，以及篩選一物質，相較於一控制組，該物質具有調控BICD1基因表現的能力。

本發明另提供一種評估一個體對一近視治療藥劑的反應，包括測定一BICD1基因之單核苷酸多型性，其中帶有該單核苷酸多型性的某些基因型時，表示該個體對該近視治療藥劑具有良好的反應(正反應)。

本發明更提供一種用於檢測近視感受性之套組，包括一或複數個試劑、一緩衝液、以及一酵素，用以偵測一或複數個BICD1基因之單核苷酸多型性。

為了讓本發明之上述和其他目的、特徵、和優點能更明顯易懂，下文特舉較佳實施例，並配合所附圖示，作詳細說明如下：

【實施方式】

在本發明一實施樣態中，本發明提供一種決定一個體是否易於罹患近視的方法，包括由一個體中獲得一生物樣本，檢測此生物樣本中BICD1基因之至少一種SNP(single

nucleotide polymorphism) 基因型，其中此 SNP 基因型的存在顯示該個體具近視感受性。此 SNP 基因型係擇自下到所組成之族群：SNPs rs7966276、rs1151029、rs2650122 及 rs10771923。此基因型的變異可為一種 BICD1 基因序列的改變，例如，可僅為單一核苷酸的改變，此改變可能會改變編碼 BICD1 基因之胜肽，導致不同的轉譯或造成基因轉錄功能受影響。

在本發明之決定是否帶有易於罹患近視及/或近視相關併發症的基因型，可使用引子延伸法(例如，PinPoint 分析, Massextend™、SPC-SBE、或 GOOD 分析)、雜交法(例如，TaqMan 分析、磁珠陣列(bead arry)、或 SNP 晶片)、ligation(例如，組成式綠螢光轉移標誌(CFET tags))，以及酵素切割(RFLP、Invader®分析)，PCR-SSCP(單鏈構象多態性)，MRD(mismatch repair dection)，BeadArray™，或 SNPlex™。首先，由一個體中採集或收集一包含核苷酸(DNA)之生物樣本。本發明所述之個體可為一哺乳動物，較佳為一罹患近視及/或近視相關併發症的人類或個體。本發明之個體包括，但不限於，成人、幼童或嬰兒。本發明之生物樣本可由任何具有染色體 DNA 之來源收集或分離而得，所謂的來源包括血液、羊水、腦脊液、或皮膚、肌肉、口腔黏膜、胎盤、腸胃道或其他器官之組織液。接著，分析 DNA 樣本中是否有易造成近視之 BICD1 基因型的存在。在本發明之一實施例中，BICD1 基因型可藉由 TaqMan 技術進行鑑定。簡單地說，利用 Primer Express version 2.0 設計 PCR 引子及 TaqMan MGB 探針，於 GeneAmp 9700 熱反應槽及 96 孔盤中進行反應，並利用

ABI Prism 7500 序列偵測系統及 ABI Prism 7500 SDS software version 1.0 偵測及分析螢光強度。在另一實施例中，可利用基因定型分析(genotyping)來鑑定 SNP 的基因型，相關流程可參照 Mutat Res 2005;573:70-82，可使用 Illumina BeadArray technology (Sentrix® Array Matrix) [Shen, 2005 #135]來進行基因定型分析。簡單地說，將特異的寡核苷酸(allelic specific oligonucleotide)黏合至 DNA 上，藉由 PCR 放大，並利用 Cy-3 及 Cy-5 標定之引子進行陣列式之雜交及及基因定型分析。在另一實施例中，可使用商品化的基因晶片來鑑定 BICD1 基因中 SNP 的基因型。例如，Affymetrix GeneChip® Human Mapping 500K 陣列套組包括二個陣列，每一個可分析約 250,000 個 SNPs，藉由一般習知的方法進行雜交，並利用 BRLMM clustering 演算法分析基因型。

此外，若基因變異(多樣性)造成限制酶切位的產生或消失，也可藉由限制酶的切割(消化)來鑑定 BICD1 基因的各基因型。首先，以 PCR 放大生物樣本中之 BICD1 基因。接著進行一 RFLP 分析。經切割的 DNA 片段可顯示出特定 BICD1 基因型的存在與否，進而得知各基因型的存在與否與近視的關係。在另一實施例中，可藉由序列分析(定序)來鑑定 BICD1 基因的各 SNP 基因型。首先利用 PCR 或其他適當的方法放大 BICD1 基因或核苷酸，接著，以一般習知的程序來分析 BICD1 核苷酸、BICD1 核苷酸片斷、BICD1 基因體 DNA、BICD1 基因體 DNA 片斷的序列，並分別比較上述核苷酸/核苷酸片斷或基因體 DNA/DNA 片斷與已知 BICD1 基因序列的差異。若有上述

基因型的存在代表此個體對近視及/或近視相關併發症具感受性。

此技藝人士可依不同情況選用不同的方法來鑑定或偵測 BICD1 基因的 SNP，且此技藝人士可輕易地了解並施行上述方法或其他方法。

本發明中所述之“近視感受性”意指為當本發明之 SNP 某一種基因型存在時，此個體容易於或不容易罹患近視。本發明中所述之“低近視感受性”意指為當本發明之 SNP 某種基因型存在時，此個體不易罹患近視。本發明中所述之“高近視感受性”意指為當本發明之 SNP 某種基因型存在時，此個體容易罹患近視。在本發明之一實施例中，當 SNP rs10771923 有對偶基因 G 基因型，或 SNP rs1151029 有對偶基因 T 之基因型存在時，表示此個體較容易罹患近視，其罹患近視的風險比其他基因型高至少 1.2 倍。在本發明另一實施例中，當 SNP rs7966276 有對偶基因 A 之基因型，其表示此個體較不容易罹患近視，其罹患近視的風險比其他基因型低至少 0.6 倍。應注意的是，此個體也會因其他因子，例如疾病或環境等而增加或減少罹患近視的風險。

在本發明另一實施樣態中，本發明提供一種篩選可治療近視及/或近視相關併發症的物質(候選藥物)，包括將一待測物質與一表現 BICD1 基因的細胞接觸，並篩選相較於對照組(未接觸候選藥物之細胞)可調控 BICD1 基因的物質。

BICD1 基因之基因型(例如，SNP rs7966276、rs1151029、rs2650122、及 rs10771923)可用來做為尋找或

鑑定治療近視及/或近視相關併發症的生物標誌。此方法是藉由篩選一可改變 BICD1 基因表現的物質。例如，將一細胞曝露於一測試物質或一混合之測試物質組合物(依序或同時)，並分析此細胞 BICD1 基因的表現，比較未處理以及經測試物質處理之細胞的 BICD1 基因表現。此測試物質可為一已知或未知之化合物。測試物質包括，但不限於，化合物、小分子藥物、聚醣類、核苷酸、蛋白質或胜肽等。例如，此測試物質可為一小分子干擾 RNA。在本發明之一實施例中，此測試物質可藉由 SNP rs10771923、SNP rs1151029 或 SNP rs7966276 的差異來影響或調控 BICD1 基因，進而抑制或減緩近視及/或近視相關併發症。

在本發明另一實施樣態中，本發明另提供一種治療、抑制或減緩近視及/或近視相關併發症的方法，包括給予一個體一有效量之近視治療劑(近視治療藥物)，此治療劑由上述方法獲得。

如上所述，藉由控制 BICD1 基因的表現或活性可抑制或誘導近視及/或近視相關併發症。因此，候選藥物可藉由調控 BICD1 基因的表現以達到治療或抑制近視及/近視相關併發症。

在本發明另一實施樣態中，本發明更提供一種評估藥物對治療近視效果的方法，包括分析 BICD1 基因的 SNP 基因型，其中若該個體存在某一特之 SNP 基因型時，表示此藥物可能對治療近視具有良好的反應。

在本發明之方法中，上述 BICD1 基因的基因標誌(基因型)可作為評估一個體對近視及/或近視相關併發症的

感受性。當一個體中存在著易罹患近視之 SNP 基因型時(例如， rs10771923 之對偶基因 G，或 SNP rs1151029 之對偶基因 T)，表示此個體可能對一近視治療藥物具有良好反應。本發明所述之“良好反應”意指與無此特定 SNP 基因型之個體相較，此個體對於此近視治療藥物具有較佳的反應，且此個體也較易於罹患近視及/或近視相關併發症。

在本發明另一實施樣態中，本發明更提供一種套組，可用於分析由一個體獲得之生物樣本，檢測此個體對近視的感受性，此套組包括一或複數個試劑以偵測 BICD1 基因中一或複數個 SNP 基因型。

本發明中所述之“套組”包括一或複數個 SNP 檢測試劑，或以一或複數種型式存在之一或複數個 SNP 檢測試劑（例如，生物試劑、容器、包裝的樣式）。本發明之 SNP 檢測套組包括，但不限於，探針及引子組合(例如，TaqMan 探針/引子組合)，核苷酸陣列/微陣列，以及包括一或複數個探針、引子或其他檢測試劑的磁珠。本發明之套組可任意地包括各種電子裝置，例如，陣列(DNA 晶片)及微流體控制系統(“lab-on-a-chip”系統)。本發明之套組可不包含電子裝置，而包括一或複數個 SNP 檢測試劑。

SNP 偵測套組一般包括一或複數個偵測試劑，及其他必須成分(例如，緩衝液、酵素，例如 DNA 聚合酶或 ligases、鏈延伸核苷酸，例如，dNTP，以及 Sanger-type DNA 定序反應物，鏈終止核苷酸，正對照組序列，負對照組序列及其類似物)以進行分析，例如，擴增及/或偵測一 SNP 核苷酸。本發明之套組更可包括一或複數個裝置以分析目

標核苷酸的含量，比較目標核苷酸與一標準含量的差異，以及包括使用說明書以說明如何使用此套組來偵測 SNP 核苷酸。在本發明之一實施例中，本發明之套組包括所需之所有試劑以偵測一或複數個 SNP 核苷酸。在本發明另一實施列中，SNP 偵測套組為一種核苷酸陣列，或間隔陣列 (compartmentalized kits)，如微流體控制系統/“lab-on-a-chip”系統。

任何適當的探針，例如對偶基因專一性探針，皆可用於上述陣列(晶片)中，且每個探針或探針對可結合至不同的對偶基因位置。聚核苷酸探針可利用光引導化學程序來形成於特定的區域。每個 DNA 晶片可包括，例如，複數個(上千至百萬個)獨立的核苷酸探針排列在微小化的格子狀裝置上。較佳此複數個探針可結合至固狀的支持陣列上。

本發明中之套組可包括，例如一或複數個試劑，一緩衝液，以及一酵素，用以檢測一或複數個 BICD1 的 SNP 基因型態。此試劑中包括至少一物質用以區別及偵測 SNP 基因型，上述物質包括，但不限於，核苷酸序列，其可完全與至少一 BICD1 的 SNP 基因型之某一位置互補，一限制酶(例如，內切酶)以鑑別一特定序列，一標定之引子或一標定的偶基因專一性探針。在本發明一實施例中，本發明用來檢測或診斷近視之套組可包括複數個引子，引子用來擴增 BICD1 基因之一區域，此區域包括 SNPs rs7966276、rs1151029、rs2650122、及/或 rs10771923，當偵測到具有高度近視感受性之 SNP 基因型時，表示此個體為近視的高危險族群。引子可分別根據 SNPs

rs7966276、rs11-51029、rs2650122 及/或 rs10771923 的兩側的序列進行設計。此外，在分析個對偶基因的差異後，可利用質譜儀、螢光或冷光來分析個對偶基因的差異。

【實施例】

1. 基因篩選

本實施例分別針對 4000 名受試者進行近視的研究。此受試者大致可分為 4 類：(1)年輕的役男，(2)大學生，(3)醫院人員，以及(4)眼科的臨床病人。若受試者一眼之屈光度≤ -6.0 D，且另一眼之屈光度≤ -4.0 D 則歸類為高度近視，而若受試者其中視力較差之一眼的屈光度≥ -1.5 D，則將此類受試當作對照組。所有受試者的年齡皆介於 17 至 45 歲，且皆為華人。

在實施的第一步驟，使用 Affymetrix GeneChip® Human Mapping 500K 晶片組，每組包括 2 個晶片，每個晶片可分析約 250,000 個 SNP(Nsp 晶片可分析約 262,000 個，Sty 晶片可分析 238,000 個)。為使 DNA 樣本維持於一適當的品質下，將所有 DNA 樣本的 OD 260/280 值控制於 1.7 至 2.0 之間，且 OD260/230 值大於 1.0，取約 1.5 μg (30 μl of 50 ng/μl)的基因體 DNA 進行基因型分析，並利用 BRLMM algorithm 以獲得基因定型分析結果。同時，為降低誤差，所有的分析必須滿足以下條件：對每個 SNP 至少 90%的樣本判讀率(per sample call rate)，每個檢體至少 90%的 SNP 判讀率(per SNP call rate)，對每個 SNP 次要對偶基因頻率至少在 1%以上，以及滿足哈溫平衡($p > 0.001$)。綜合上述結果，對 SNP rs380619 進行進一步的分

析。

接著利用 PLINK program (*Am J Hum Genet* 2007;81:559-75)來計算基因型及對偶基因頻率，及進行 χ^2 測試，以分析對偶基因、SNP 基因型與高度近視之間的關係。

為了在各種遺傳模式下分析基因型的關係，將所獲得的基因定型分析數據置入顯性(dominant)、隱性(recessive)及加成性(additive)模式，並進行 trend 測試。將包含各種變因(性別及年齡)之基因效應導入迴歸分析中，並利用線性回歸模式來分析各個 SNP 與屈光度的關係。由於屈光度大於-3D 的情況普遍發生於台灣人上，因此又將受試者分為正常/中度近視(≧-3D)以及高度近視(≦ -6 D)二種，並以邏輯迴歸(Logistic Regression)分析表現型。並利用 Hap-clustering 來分析單體型(haplotype)。

本實施例之初步分析顯示出 10 個最相關的 SNPs，且其中 p 值最小為 0.0002。此 10 個 SNPs 分別位於染色體 1、2、4、6、12、16、17 及 21，且分別座落於不相鄰的位置。

2. 基因篩選之第二步驟

在本實施例的第二步驟，首先利用由晶片篩選出的 10 個最相關的 SNPs，並在每個 SNP 的前後端 200 kb 區域當成是候選區域。在這 10 個區域我們選了 384 個 SNP，在 1536 位受試者進行基因型鑑定。此 1536 位受試者之屈光度分別< -6 D 或> -1.5D。基因型鑑定是用 Illumina BeadArray technology (Sentrix® Array Matrix) (Mutat Res 2005;573:70-82)的操作平台，此平台利用 DNA 會與對偶

基因特異性寡核苷酸黏合，並經由 PCR 程序放大。晶片的雜交程序及基因定位分析分別利用經 Cy-3 及 Cy-5 標定的引子所完成。每個 SNP 重複 30 次以計算最高的基因頻率。

整體來看，在此第二步驟中的基因鑑定的成功率為 97.1%。我們發現最相關的 SNP (rs7966276)位於染色體 12p11 的 BICD1 基因上，其 p 值< $1.13x10^{-04}$，且 BICD1 基因中其他的 SNPs 同樣具有高度的相關性(SNP rs1151029, p= $4.78x10^{-4}$; SNP rs2650122, p= $3.65x10^{-2}$; SNP rs10771923, p= $2.70x10^{-2}$)。

3. 基因篩選之第三步驟

在第三步驟中，利用 TaqMan 技術(Applied Biosystems [ABI], Foster City, USA)來分析由第二步驟中所獲得之高度相關的 SNPs。簡而言之，以 Primer Express version 2.0 設計 PCR 引子及 TaqMan MGB 探針，在 96 孔盤及 GeneAmp 9700 thermal cyclers 反應槽中完成反應，並利用 ABI Prism 7500 序列偵測系統及 ABI Prism 7500 SDS software version 1.0 軟體來偵測及分析螢光強度。在此第三步驟中，所有受試者不論其屈光度之 DNA 都進行 SNP 基因型鑑定。

在第三步驟中，主要聚焦於 BICD1 基因，並以不同的遺傳模式分析超過 3000 位受試者之 SNP rs10771923、SNP rs1151029、及 SNP rs7966276 的基因效應，各個 SNP 的基因頻率如表一所示。參照表二，當 rs10771923 的次要對偶基因 G 具有加成效應(p = 0.00088, OR=1.22)或

rs1151029 的次要對偶基因 T 具有顯性有害效應(dominant deleterious)時可在二種表現型(以≧-3D 作為對照組，以≦-6 D 作為近視)中獲得最相關的結果，而 SNP rs7966276 與近視的相關性較其他二個 SNPs 來得低。當以近視度數當成連續變數分析後，此 3 個 SNPs 顯示出有意義的結果，如表三所示。第 1 圖顯示 SNP rs1151029 對偶基因 T 之頻率與各屈光度的關係，橫軸代表屈光度。

表一、對偶基因頻率及 BICD1 基因定型型分析

	rs10771923		rs1151029		rs7966276	
屈光度	樣本數	MAF	樣本數	MAF	樣本數	MAF
≧ -3 D	1305	0.375	0630	0.211	1215	0.040
-3D 至-6 D	941	0.400	1148	0.228	953	0.027
≦ -6 D	1027	0.423	1139	0.247	794	0.025
總合	3273	0.397	3917	0.226	2962	0.032

MAF(minor allele frequency):次要對偶基因頻率

表二、以邏輯迴歸分析二元特徵(正常/中度近視 vs. 高度近視)

	基因型			OR (p 值)			
	N (%)	N (%)	N (%)	總合	加成性	顯性	隱性
rs10771923	AA	AG	GG				
≧-3 D	509 (39.0)	614 (47.1)	182 (14.0)	1305	1.22 (0.00088)	1.30 (0.0024)	1.30 (0.021)
≦-6 D	338 (32.9)	510 (49.7)	179 (17.4)	1027			
rs1151029	AA	AT	TT				
≧-3 D	1027 (63.0)	519 (31.8)	84 (5.15)	1630	1.22 (0.0017)	1.30 (0.00088)	1.21 (0.263)
≦-6 D	646 (56.7)	423 (37.1)	70 (6.14)	1139			
rs7966276	TT	AT	AA				
≧-3 D	1122 (92.3)	90 (7.40)	3 (0.24)	1215	0.61 (0.0114)	0.62 (0.0161)	
≦-6 D	755 (95.0)	39 (4.91)	0 (0)	794			

表三、以線性回歸模式分析屈光度

基因型		加成性		顯性		隱性	
	p 值	β x 100	p 值	B x 100	p 值	B x 100	p 值
rs10771923	0.0128	48.4	0.0032	29.2	0.0115	35.4	0.0230
rs1151029	0.020	46.9	0.0060	28.8	0.0060	29.6	0.181
rs7966276	0.022	-125.1	0.0060	-62.7	0.0077	-173.8	0.260

雖然本發明已以較佳實施例揭露如上，然其並非用以限定本發明，任何熟習此技藝者，在不脫離本發明之精神和範圍內，當可作些許之更動與潤飾，因此本發明之保護範圍當視後附之申請專利範圍所界定者為準。

【圖式簡單說明】

第 1 圖顯示 rs1151029 對偶基因 T 之頻率與各個屈光度的關係。

【主要元件符號說明】

無。

序列表

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<120> 決定個體罹患高度近視的風險性之方法

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gctgccgagt acgggctggt ggtgctggag gagaagctga ccctcaaaca gcagtatgat 240
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七、申請專利範圍：

1.一種決定一個體罹患高度近視的風險性之方法，包括：

由該個體中獲得一生物樣本，以及

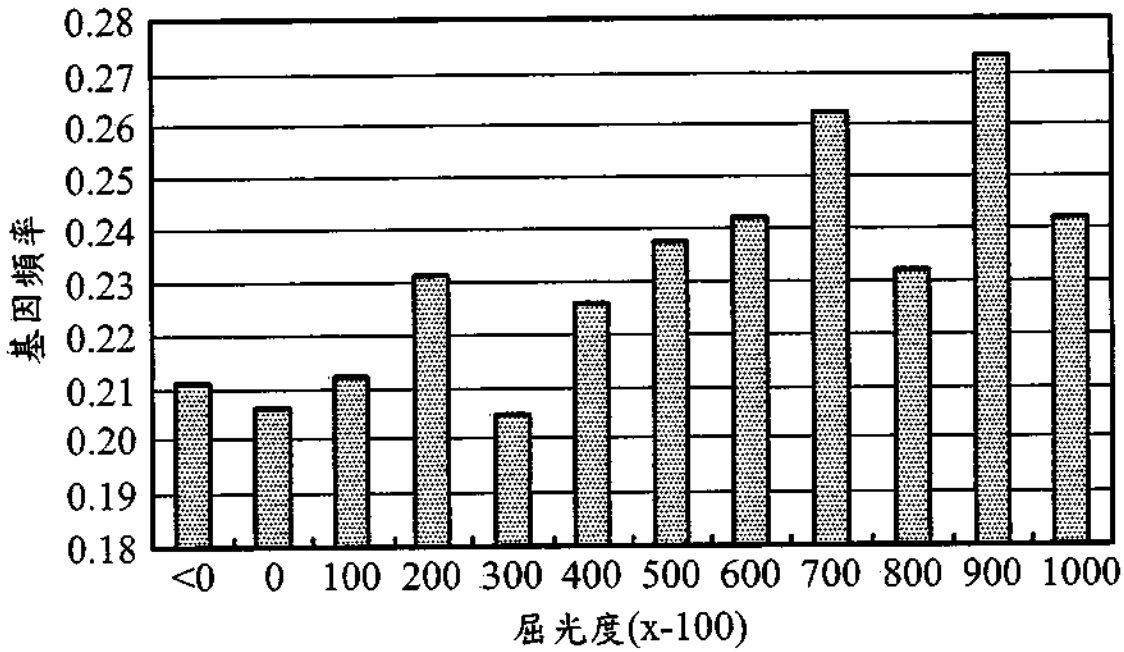
測定該生物樣本中的 BICD1 基因(序列識別號 1)之單核苷酸多型性 SNP rs7966276(A/T)、SNP rs1151029(A/T)或 SNP rs10771923 (A/G)之至少一種，

其中，當 SNPs rs7966276(A/T)被偵測為 TT 基因型、SNPs rs1151029(A/T)被偵測為 TT 基因型、或 SNPs rs10771923 (A/G)被偵測為 GG 基因型時，表示該個體罹患高度近視的風險性增加，

其中，該高度近視為屈光度≦-6D。

2.如申請專利範圍第 1 項所述之決定一個體罹患高度近視的風險性之方法，其中該個體為一哺乳動物。

3.如申請專利範圍第 1 項所述之決定一個體罹患高度近視的風險性之方法，其中該生物樣本選自於血液、羊水、腦脊液、或來自皮膚、肌肉、結膜、胎盤或腸胃道之組織液所組成之群。



第 1 圖