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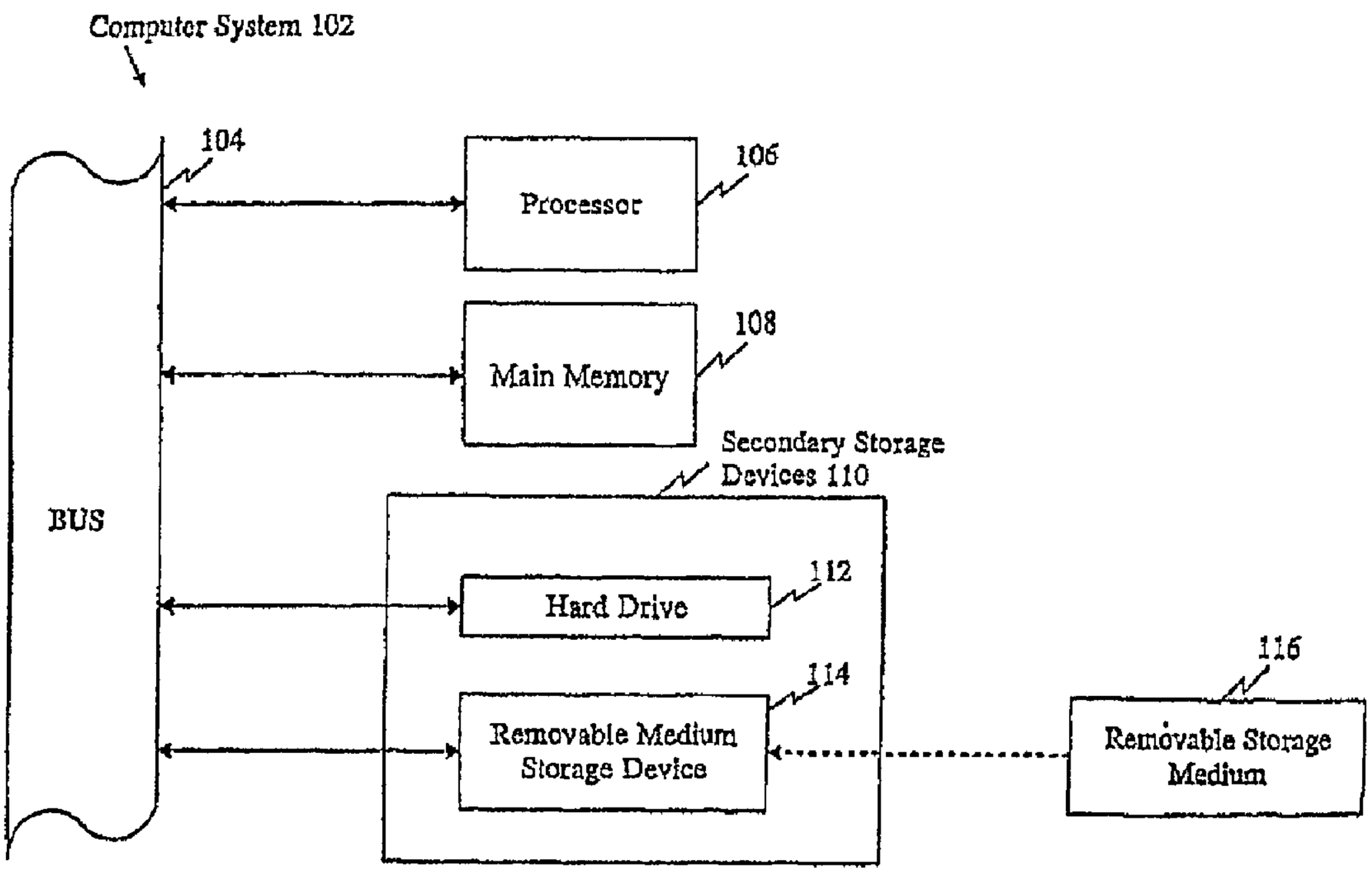
(54) Titre : POLYMORPHISMES GENETIQUES ASSOCIES A L'INFARCTUS DU MYOCARDE, TECHNIQUES DE DETECTION ET UTILISATIONS DE CEUX-CI

(54) Title: GENETIC POLYMORPHISMS ASSOCIATED WITH MYOCARDIAL INFARCTION, METHODS OF DETECTION AND USES THEREOF



(57) Abrégé/Abstract:
The present invention is based on the discovery of genetic polymorphisms that are associated with myocardial infarction. In particular, the present invention relates to nucleic acid molecules containing the polymorphisms, variant proteins encoded by such nucleic acid molecules, reagents for detecting the polymorphic nucleic acid molecules and proteins, and methods of using the nucleic acid and proteins as well as methods of using reagents for their detection. Figure 1 provides a diagrammatic representation of a computer-based discovery system containing the SNP information of the present invention in computer readable form.

Abstract

The present invention is based on the discovery of genetic polymorphisms that are associated with myocardial infarction. In particular, the present invention relates to nucleic acid molecules containing the polymorphisms, variant proteins encoded by such nucleic acid molecules, reagents for detecting the polymorphic nucleic acid molecules and proteins, and methods of using the nucleic acid and proteins as well as methods of using reagents for their detection.

Figure 1 provides a diagrammatic representation of a computer-based discovery system containing the SNP information of the present invention in computer readable form.

Claims:

1. A method for identifying an individual who has an altered risk for developing myocardial infarction, comprising detecting a single nucleotide polymorphism (SNP) in any one of the nucleotide sequences of SEQ ID NOs:1-206, 209-828, 1657-4398, 4400-6796, 6798-6814, 6816-17617 and 17619-73085 in said individual's nucleic acids, wherein the presence of the SNP is correlated with an altered risk for myocardial infarction in said individual.

2. An isolated nucleic acid molecule comprising at least 8 contiguous nucleotides wherein one of the nucleotides is a single nucleotide polymorphism (SNP) selected from any one of the nucleotide sequences in SEQ ID NOs: 1-206, 209-828, 1657-4398, 4400-6796, 6798-6814, 6816-17617 and 17619-73085, or a complement thereof.

3. An isolated nucleic acid molecule that encodes any one of the amino acid sequences in SEQ ID NOs:829-1019, 1021-1034 and 1037-1656.

4. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:829-1019, 1021-1034 and 1037-1656.

5. An antibody that specifically binds to a polypeptide of claim 4, or an antigen-binding fragment thereof.

6. An amplified polynucleotide containing a single nucleotide polymorphism (SNP) selected from any one of the nucleotide sequences of SEQ ID NOs:1-206, 209-828, 1657-4398, 4400-6796, 6798-6814, 6816-17617 and 17619-73085, or a complement thereof, wherein the amplified polynucleotide is between about 16 and about 1,000 nucleotides in length.

7. An isolated polynucleotide which specifically hybridizes to a nucleic acid molecule containing a single nucleotide polymorphism (SNP) in any one of the nucleotide sequences in SEQ ID NOs:1-206, 209-828, 1657-4398, 4400-6796, 6798-6814, 6816-17617 and 17619-73085.

8. A kit for detecting a single nucleotide polymorphism (SNP) in a nucleic acid, comprising the polynucleotide of claim 7, a buffer and an enzyme.

9. A method of detecting a single nucleotide polymorphism (SNP) in a nucleic acid molecule, comprising contacting a test sample with a reagent which specifically hybridizes to a SNP in any one of the nucleotide sequences of SEQ ID NOs:1-206, 209-828, 1657-4398, 4400-6796, 6798-6814, 6816-17617 and 17619-73085 under stringent hybridization conditions, and detecting the formation of a hybridized duplex.

10. A method of detecting a variant polypeptide, comprising contacting a reagent with a variant polypeptide encoded by a single nucleotide polymorphism (SNP) in any one of the nucleotide sequences of SEQ ID NOs:1-206, 209-828, 1657-4398, 4400-6796, 6798-6814, 6816-17617 and 17619-73085 in a test sample, and detecting the binding of the reagent to the polypeptide.

11. A method for identifying an agent useful in therapeutically or prophylactically treating myocardial infarction, comprising contacting the polypeptide of claim 4 with a candidate agent under conditions suitable to allow formation of a binding complex between the polypeptide and the candidate agent, and detecting the formation of the binding complex, wherein the presence of the complex identifies said agent.

12. A method for determining a human's risk for myocardial infarction (MI), the method comprising testing nucleic acid from said human for the presence or absence of a polymorphism in gene *WDR12* at position 101 of SEQ ID NO:25288 or its complement, wherein the presence of G at position 101 of SEQ ID NO:25288 or C at position 101 of its complement indicates that said human has an increased risk for MI.

13. The method of claim 12, wherein said nucleic acid is a nucleic acid extract from a biological sample from said human.

14. The method of claim 13, wherein said biological sample comprises blood, saliva, or buccal cells.

15. The method of claim 13 or 14, further comprising preparing said nucleic acid extract from said biological sample prior to said testing.

16. The method of any one of claims 12 to 15, wherein said testing comprises nucleic acid amplification.

17. The method of claim 16, wherein said nucleic acid amplification is carried out by polymerase chain reaction (PCR).

18. The method of any one of claims 12 to 17, further comprising correlating the presence of said G or said C with an increased risk for MI, or correlating the absence of said G or said C with no increased risk for MI.

19. The method of claim 18, wherein said correlating is performed by computer software.

20. The method of any one of claims 12 to 19, wherein said testing is performed using sequencing, 5' nuclease digestion, molecular beacon assay, oligonucleotide ligation assay (OLA), size analysis, single-stranded conformation polymorphism (SSCP) analysis, or denaturing gradient gel electrophoresis (DGGE).

21. The method of any one of claims 12 to 19, wherein said testing is performed using an allele-specific method.

22. The method of claim 21, wherein said allele-specific method is allele-specific probe hybridization, allele-specific primer extension, or allele-specific amplification.

23. The method of claim 21 or 22, wherein said allele-specific method is carried out using an allele-specific primer comprising SEQ ID NO:73593 or SEQ ID NO:73594.

24. The method of any one of claims 12 to 23, wherein said human is homozygous for said G or said C.

25. The method of any one of claims 12 to 23, wherein said human is heterozygous for said G or said C.

26. An allele-specific polynucleotide for use in a method as defined in any one of claims 12 to 25, wherein said polynucleotide specifically hybridizes to said polymorphism in which said G or said C is present.

27. An allele-specific polynucleotide for use in a method as defined in any one of claims 12 to 25, wherein said polynucleotide comprises a segment of SEQ ID NO: 25288 or its complement at least 16 nucleotides in length that includes said position 101.

28. The allele-specific polynucleotide of claim 26 or 27, wherein said polynucleotide is detectably labeled.

29. The allele-specific polynucleotide of claim 28, wherein said polynucleotide is labeled with a florescent dye.

30. A kit for use in a method as defined in any one of claims 12 to 25, wherein said kit comprises at least one polynucleotide as defined in any one of claims 26 to 29 and at least one further component, wherein the at least one further component is a buffer, deoxynucleotide triphosphates (dNTPs), and amplification primer pair, an enzyme or any combination thereof.

31. The kit of claim 30, wherein said enzyme is a polymerase or a ligase.

32. A method for determining a human's risk for myocardial infarction (MI), the method comprising testing nucleic acid from said human for the presence or absence of a polymorphism in gene *ATF6* at position 101 of SEQ ID NO:19038 or its complement, wherein the presence of C at position 101 of SEQ ID NO:19038 or G at position 101 of its complement indicates that said human has an increased risk for MI.

33. The method of claim 32, wherein said nucleic acid is a nucleic acid extract from a biological sample from said human.

34. The method of claim 33, wherein said biological sample comprises blood, saliva, or buccal cells.

35. The method of claim 33 or 34, further comprising preparing said nucleic acid extract from said biological sample prior to said testing.

36. The method of any one of claims 32 to 35, wherein said testing comprises nucleic acid amplification.

37. The method of claim 36, wherein said nucleic acid amplification is carried out by polymerase chain reaction (PCR).

38. The method of any one of claims 32 to 37, further comprising correlating the presence of said C or said G with an increased risk for MI, or correlating the absence of said C or said G with no increased risk for MI.

39. The method of claim 38, wherein said correlating is performed by computer software.

40. The method of any one of claims 32 to 39, wherein said testing is performed using sequencing, 5' nuclease digestion, molecular beacon assay, oligonucleotide ligation assay (OLA), size analysis, single-stranded conformation polymorphism (SSCP) analysis, or denaturing gradient gel electrophoresis (DGGE).

41. The method of any one of claims 32 to 39, wherein said testing is performed using an allele-specific method.

42. The method of claim 41, wherein said allele-specific method is allele-specific probe hybridization, allele-specific primer extension, or allele-specific amplification.

43. The method of claim 41 or 42, wherein said allele-specific method is carried out using an allele-specific primer comprising SEQ ID NO:73557 or SEQ ID NO:73558.

44. The method of any one of claims 32 to 43, wherein said human is homozygous for said C or said G.

45. The method of any one of claims 32 to 43, wherein said human is heterozygous for said C or said G.

46. An allele-specific polynucleotide for use in a method as defined in any one of claims 32 to 45, wherein said polynucleotide specifically hybridizes to said polymorphism in which said G or said C is present.

47. An allele-specific polynucleotide for use in a method as defined in any one of claims 32 to 45, wherein said polynucleotide comprises a segment of SEQ ID NO: 19038 or its complement at least 16 nucleotides in length that includes said position 101.

48. The allele-specific polynucleotide of claim 46 or 47, wherein said polynucleotide is detectably labeled.

49. The allele-specific polynucleotide of claim 48, wherein said polynucleotide is labeled with a florescent dye.

50. A kit for use in a method as defined in any one of claims 32 to 45, wherein said kit comprises at least one polynucleotide as defined in any one of claims 46 to 49 and at least one further component, wherein the at least one further component is a buffer, deoxynucleotide triphosphates (dNTPs), and amplification primer pair, an enzyme or any combination thereof.

51. The kit of claim 50, wherein said enzyme is a polymerase or a ligase.

52. A method for determining a human's risk for myocardial infarction (MI), the method comprising testing nucleic acid from said human for the presence or absence of a polymorphism in gene *PROCR* at position 101 of SEQ ID NO:54323 or its complement, wherein the presence of G at position 101 of SEQ ID NO:54323 or C at position 101 of its complement indicates that said human has an increased risk for MI.

53. The method of claim 52, wherein said nucleic acid is a nucleic acid extract from a biological sample from said human.

54. The method of claim 53, wherein said biological sample comprises blood, saliva, or buccal cells.

55. The method of claim 53 or 54, further comprising preparing said nucleic acid extract from said biological sample prior to said testing.

56. The method of any one of claims 52 to 55, wherein said testing comprises nucleic acid amplification.

57. The method of claim 56, wherein said nucleic acid amplification is carried out by polymerase chain reaction (PCR).

58. The method of any one of claims 52 to 57, further comprising correlating the presence of said G or said C with an increased risk for MI, or correlating the absence of said G or said C with no increased risk for MI.

59. The method of claim 58, wherein said correlating is performed by computer software.

60. The method of any one of claims 52 to 59, wherein said testing is performed using sequencing, 5' nuclease digestion, molecular beacon assay, oligonucleotide ligation assay (OLA), size analysis, single-stranded conformation polymorphism (SSCP) analysis, or denaturing gradient gel electrophoresis (DGGE).

61. The method of any one of claims 52 to 59, wherein said testing is performed using an allele-specific method.

62. The method of claim 61, wherein said allele-specific method is allele-specific probe hybridization, allele-specific primer extension, or allele-specific amplification.

63. The method of claim 61 or 62, wherein said allele-specific method is carried out using an allele-specific primer comprising SEQ ID NO:73542 or SEQ ID NO:73543.

64. The method of any one of claims 52 to 63, wherein said human is homozygous for said G or said C.

65. The method of any one of claims 52 to 63, wherein said human is heterozygous for said G or said C.

66. An allele-specific polynucleotide for use in a method as defined in any one of claims 52 to 65, wherein said polynucleotide specifically hybridizes to said polymorphism in which said G or said C is present.

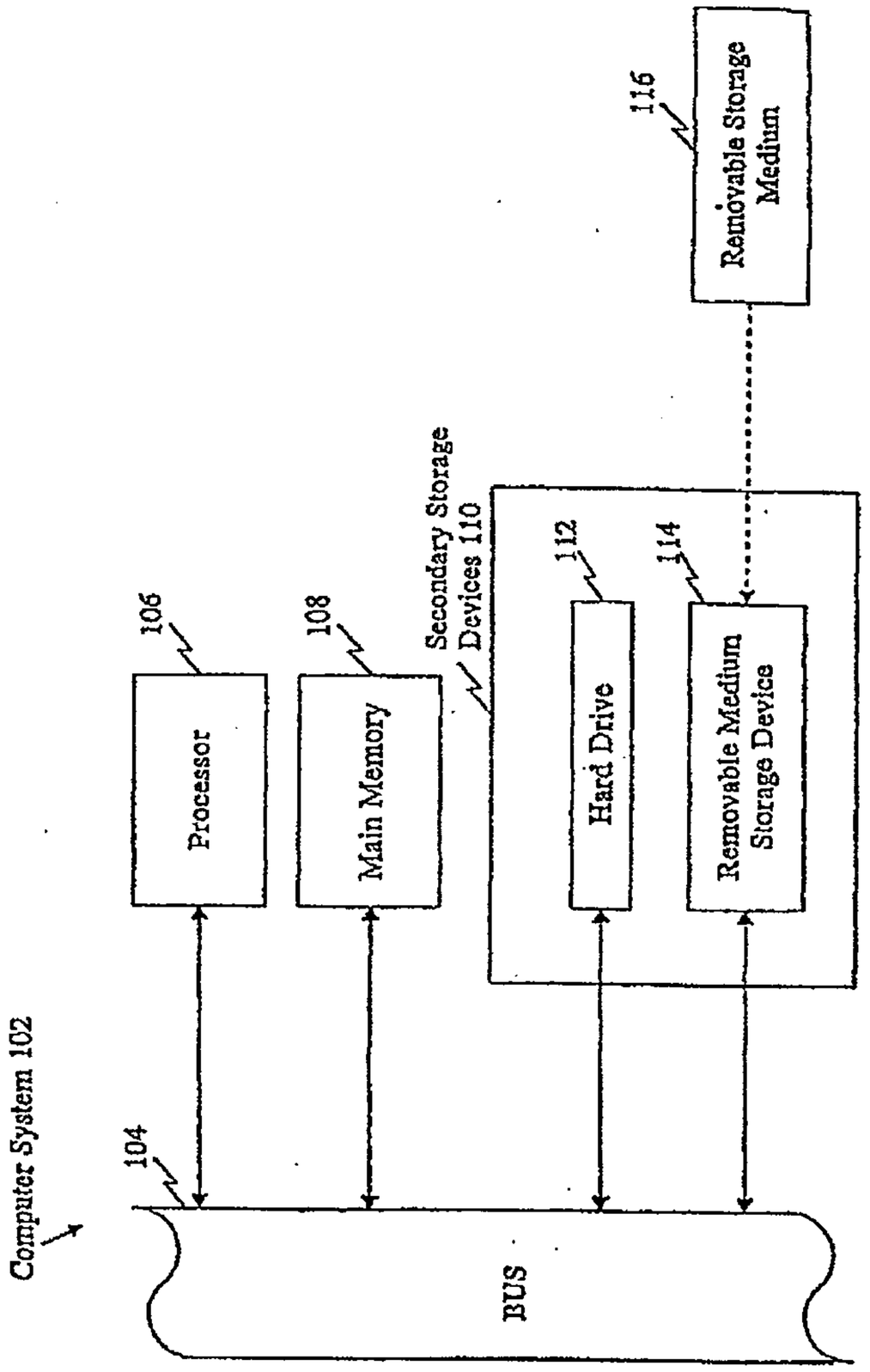
67. An allele-specific polynucleotide for use in a method as defined in any one of claims 52 to 65, wherein said polynucleotide comprises a segment of SEQ ID NO: 54323 or its complement at least 16 nucleotides in length that includes said position 101.

68. The allele-specific polynucleotide of claim 66 or 67, wherein said polynucleotide is detectably labeled.

69. The allele-specific polynucleotide of claim 68, wherein said polynucleotide is labeled with a florescent dye.

70. A kit for use in a method as defined in any one of claims 52 to 65, wherein said kit comprises at least one polynucleotide as defined in any one of claims 66 to 69 and at least one further component, wherein the at least one further component is a buffer, deoxynucleotide triphosphates (dNTPs), and amplification primer pair, an enzyme or any combination thereof.

71. The kit of claim 70, wherein said enzyme is a polymerase or a ligase.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Hard Drive
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Removable Medium Storage Device
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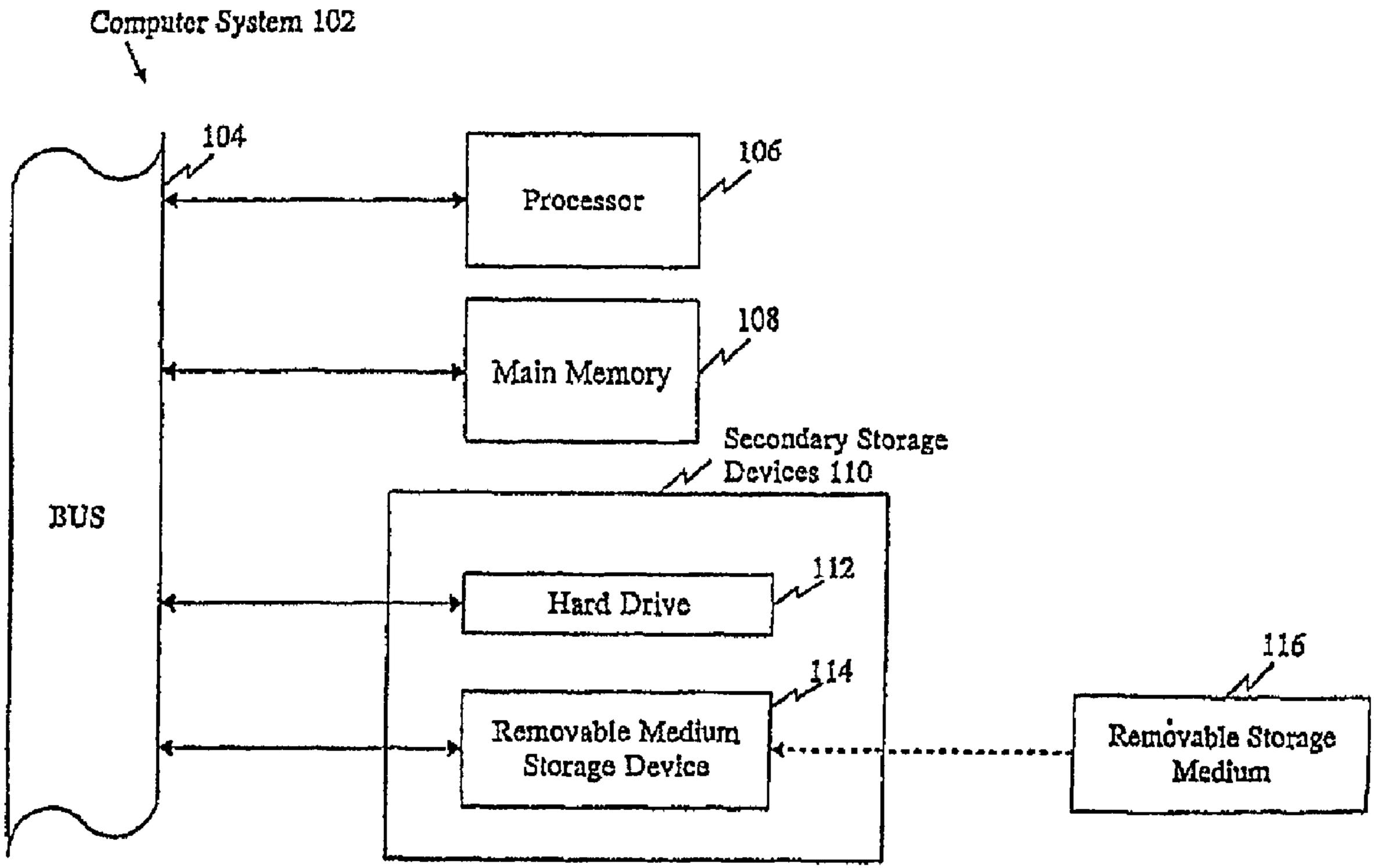
Removable Storage Medium

FIGURE 1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