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Supplemental Data

A Rare Variant Nonparametric Linkage Method for Nuclear and Extended Pedigrees with Application to Late-Onset Alzheimer Disease via WGS Data

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Supplemental Material

Supplemental Figures and Tables

Figure S1. Pedigree structures used for evaluation of intra-familial locus heterogeneity

Pedigrees with intra-familial locus heterogeneity were simulated by generating genotypes on extended families with two branches with three of the four children in the last generation being affected (panel A) and analyzing pedigrees with all children affected (panel B), to mimic intra intra-familial locus heterogeneity

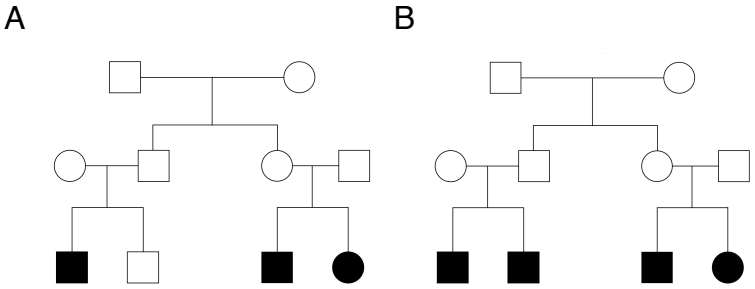
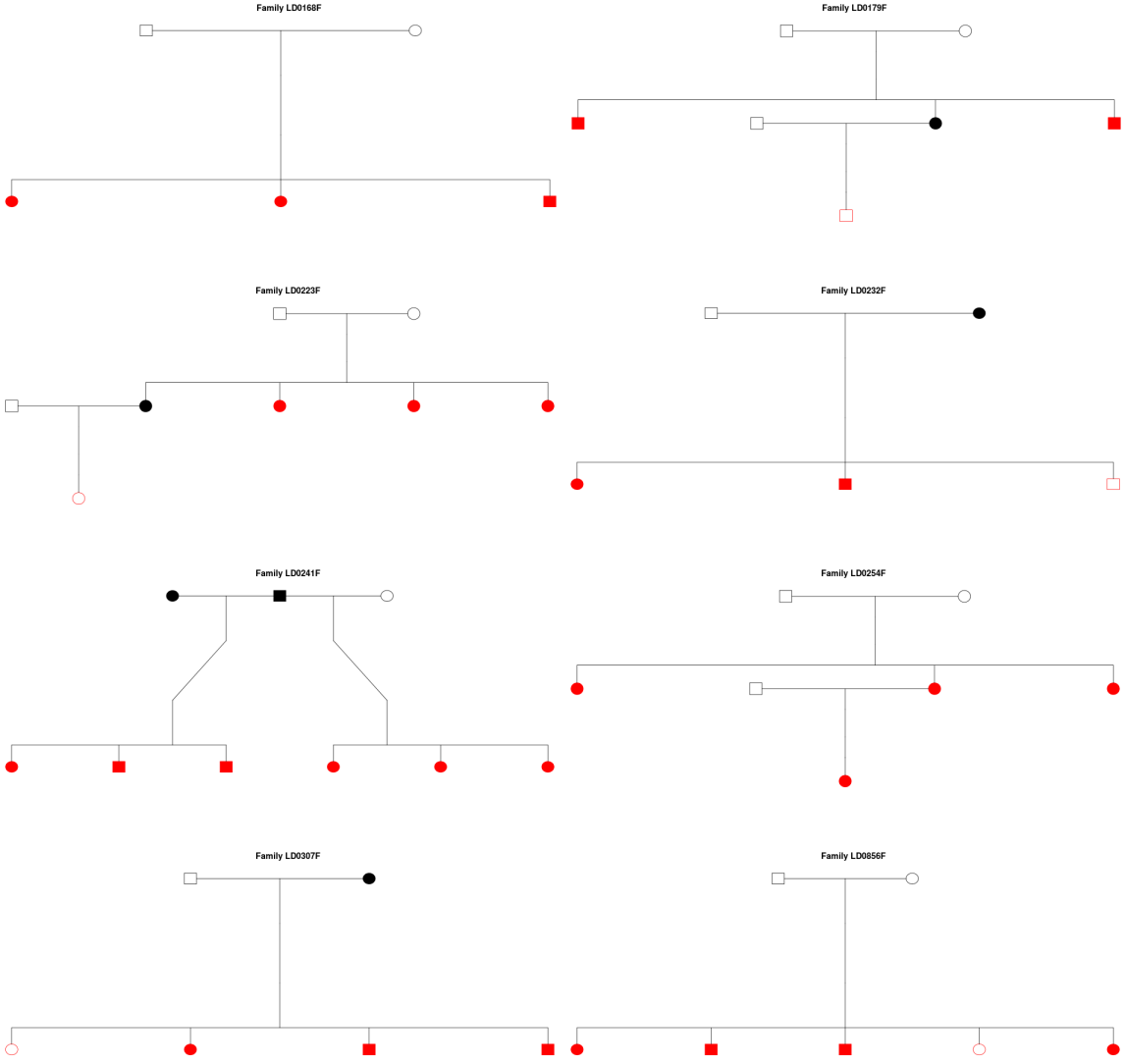


Figure S2. Pedigrees included in the analysis from the Alzheimer's Disease Sequencing Project

The 107 pedigrees (42 European pedigrees and 65 Hispanic pedigrees) which were analyzed. Squares represent males and circles females. Filled symbols are individuals affected Alzheimer's disease and open symbols represent unaffected family members. Those individuals shown in red have whole genome sequence data available, while those in black do not have available genotype data.

1. European pedigrees



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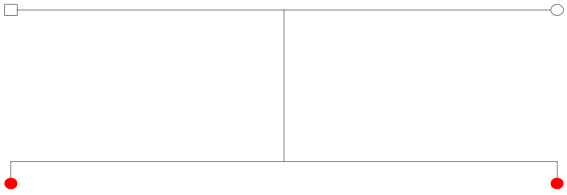

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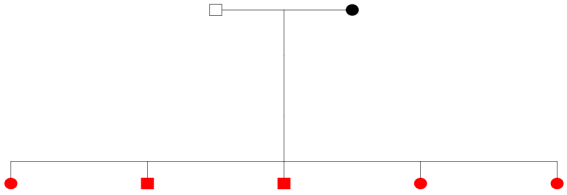

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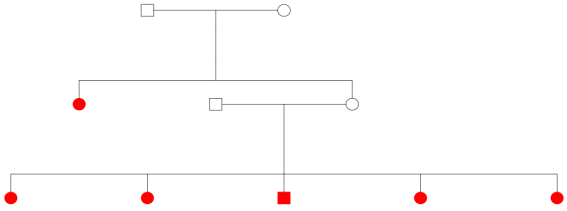

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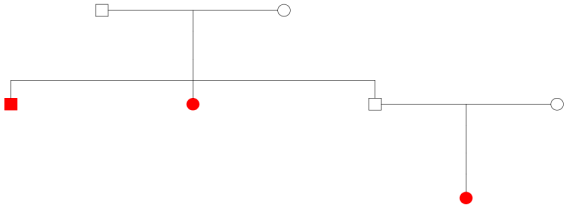

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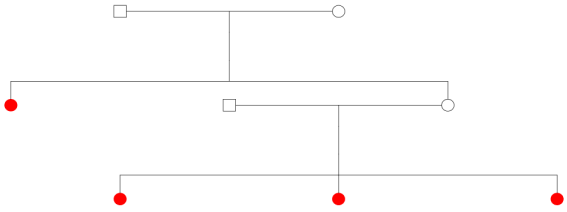

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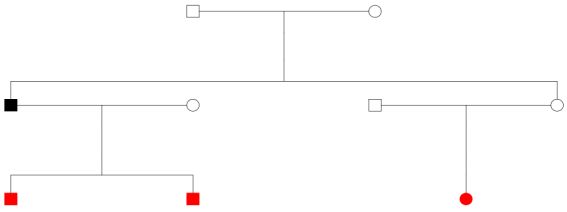

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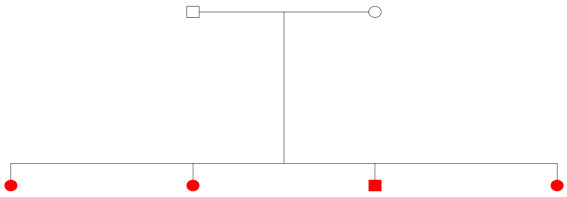

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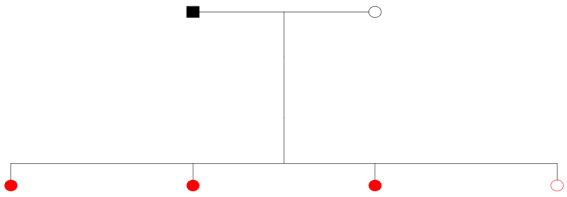

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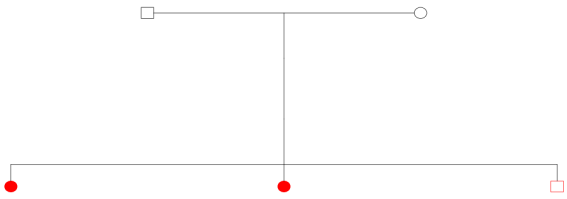

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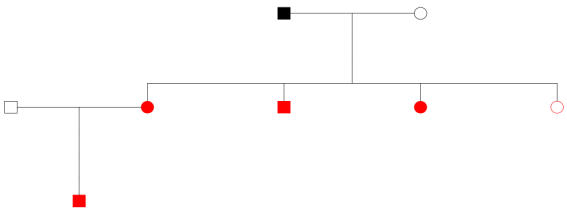

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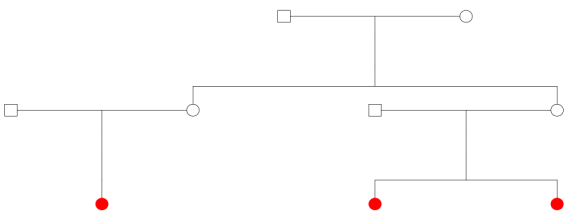

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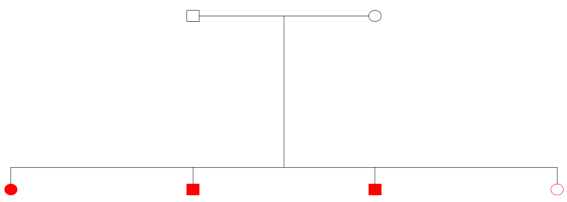

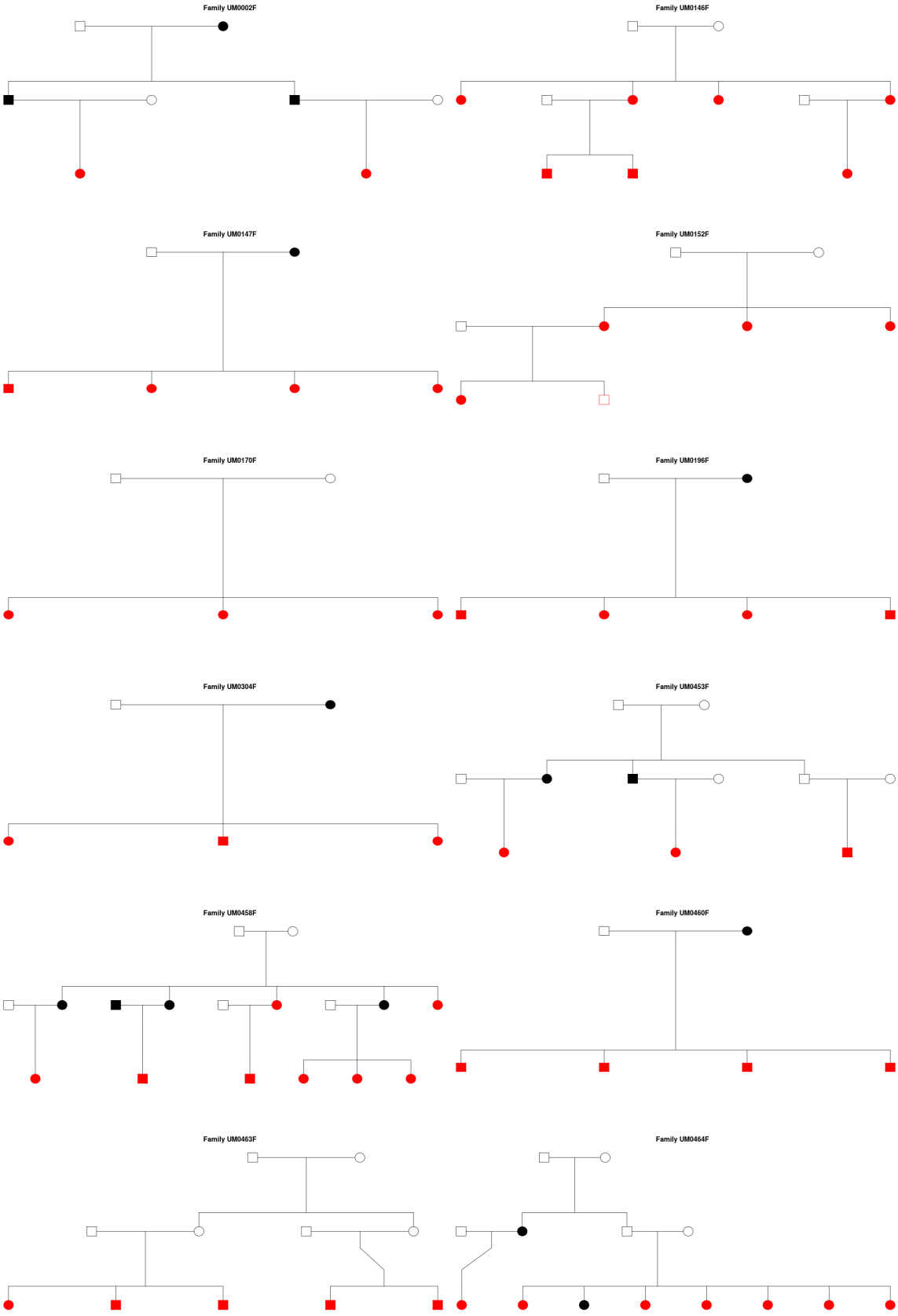
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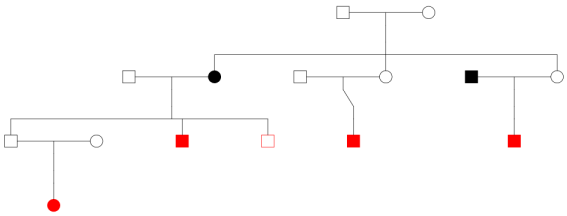

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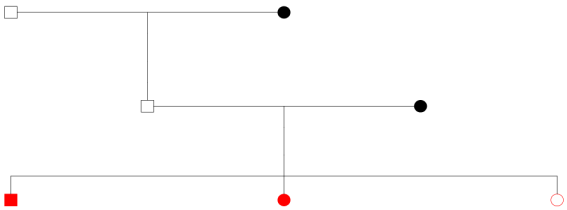

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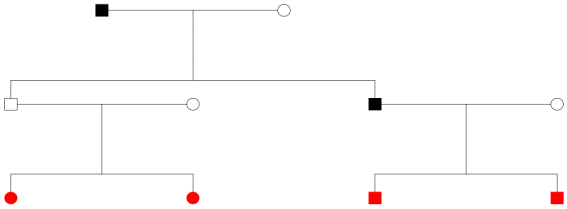

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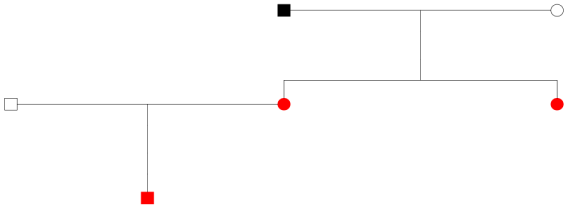

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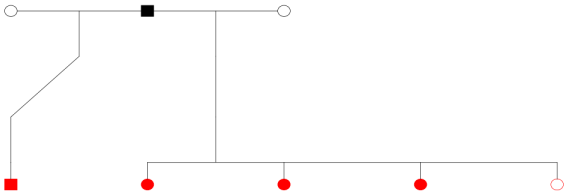

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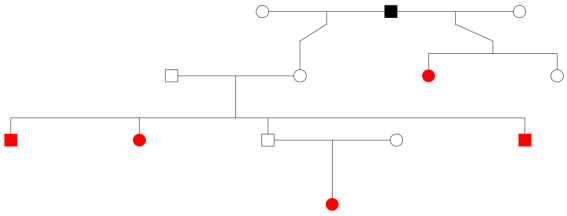

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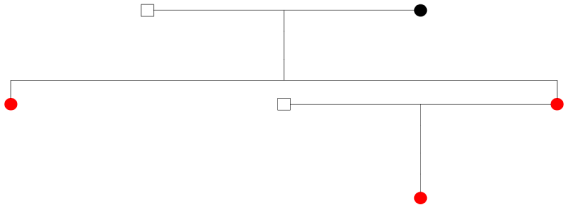

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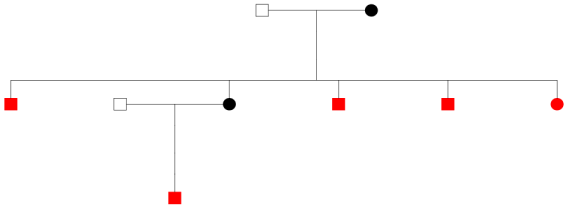

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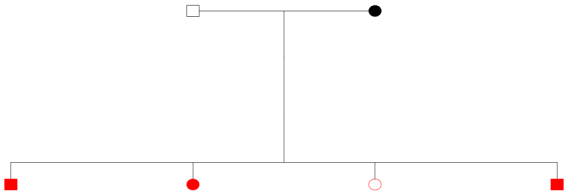

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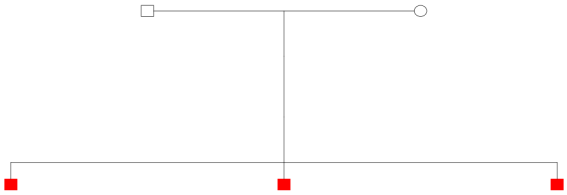
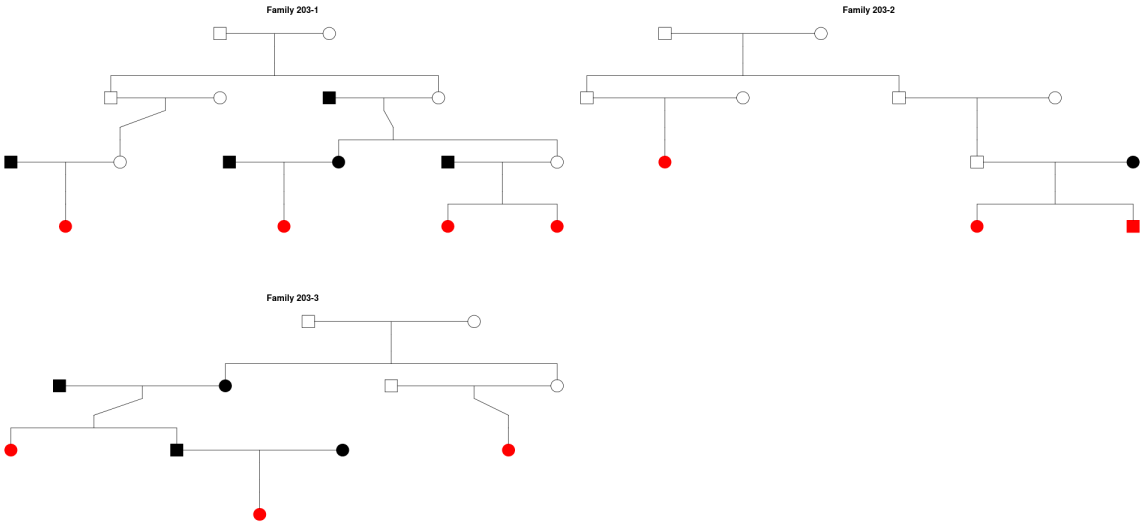
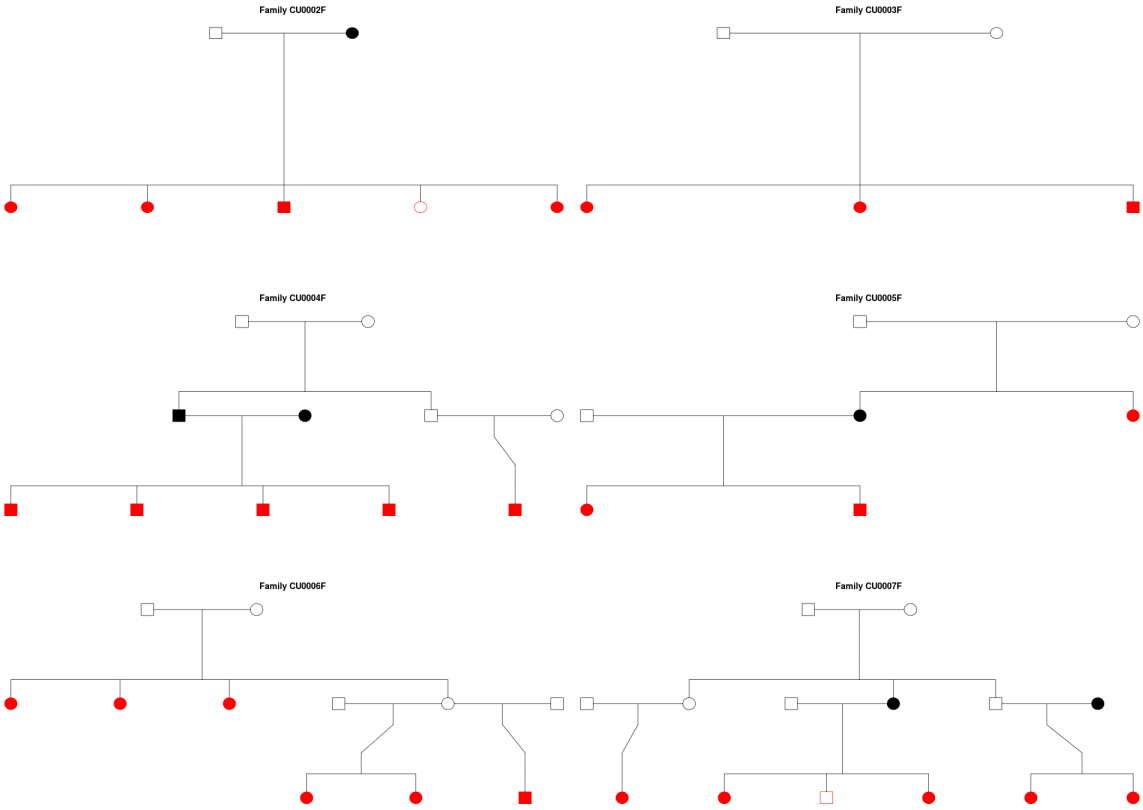




2. Hispanic Pedigrees



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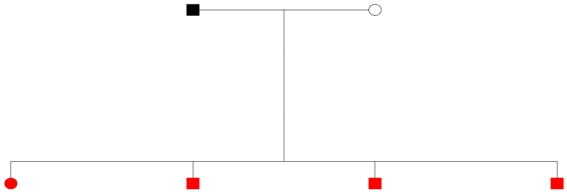

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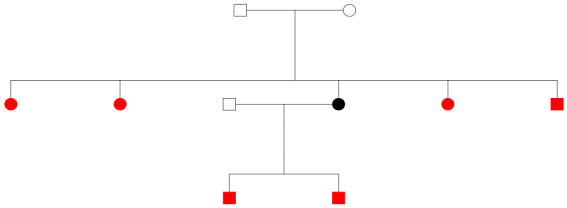

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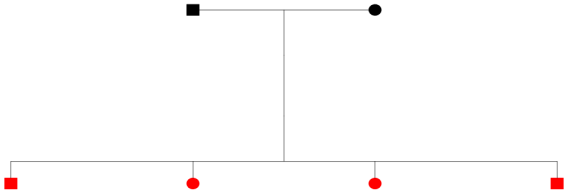

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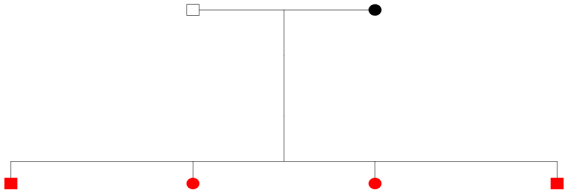

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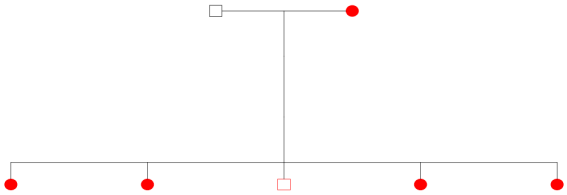

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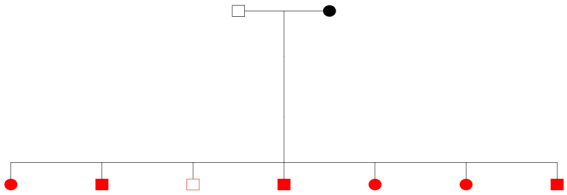

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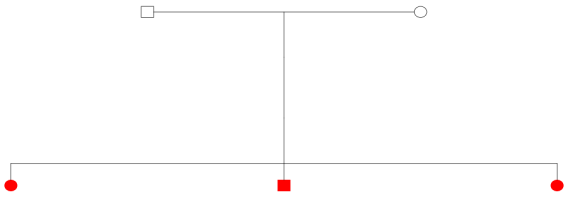

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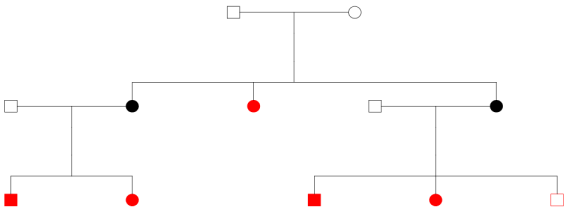

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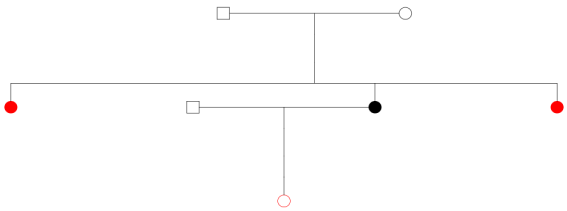

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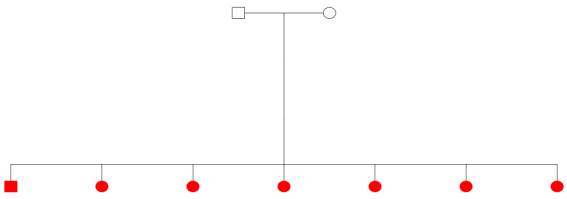

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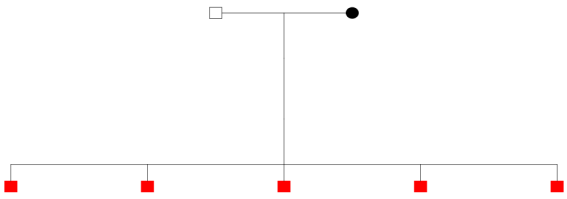

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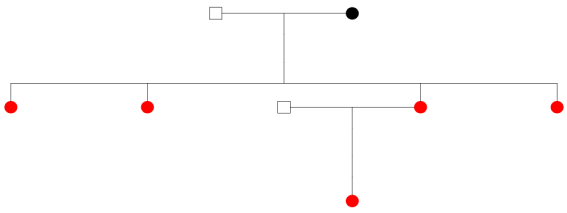

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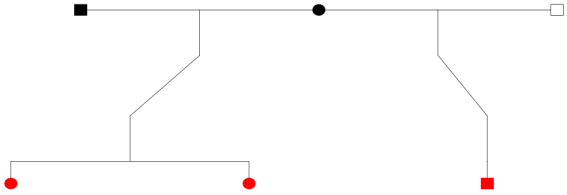

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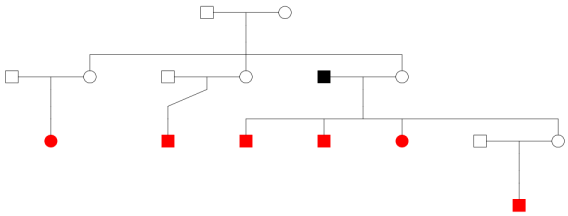

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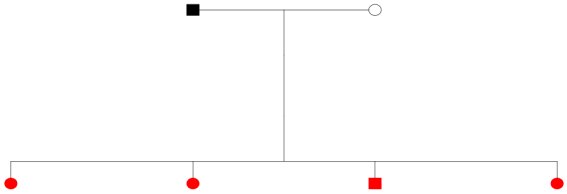

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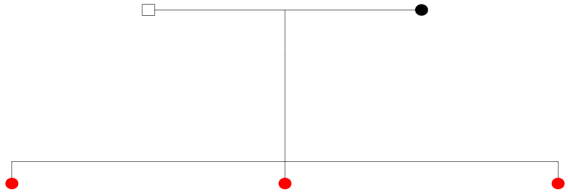

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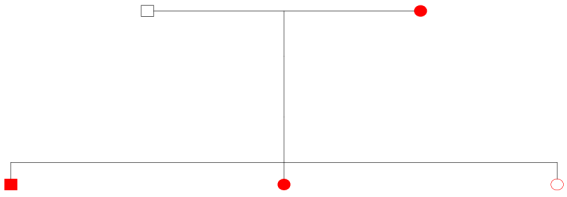

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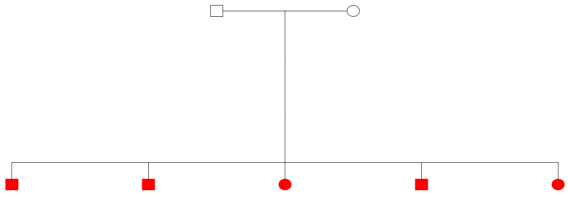

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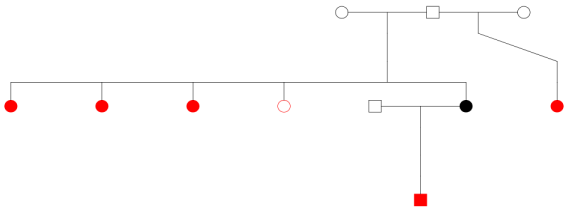

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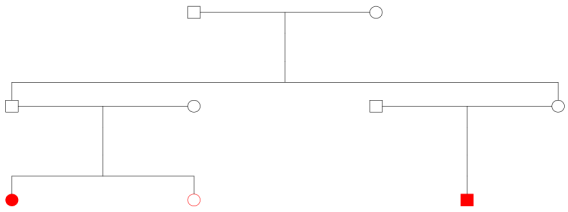

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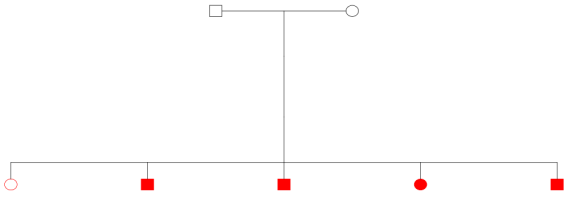

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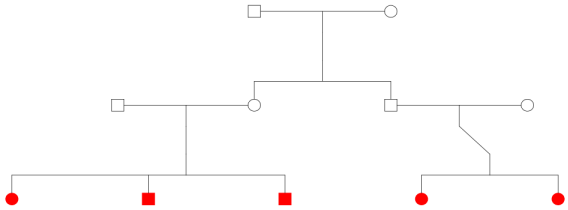

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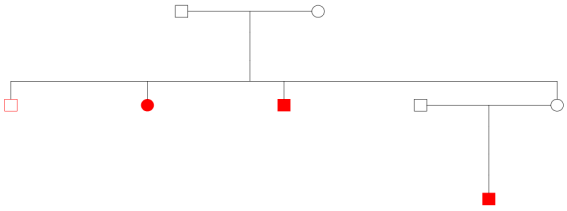

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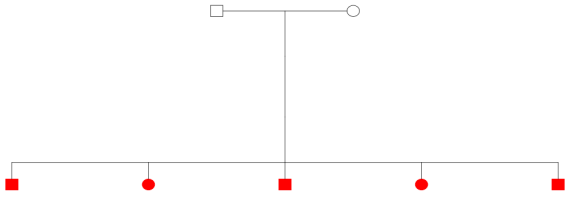

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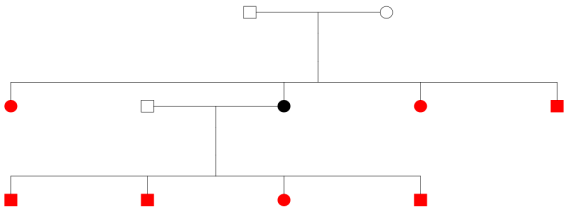

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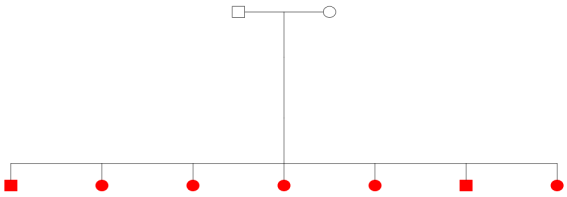

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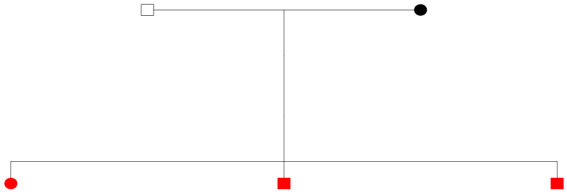

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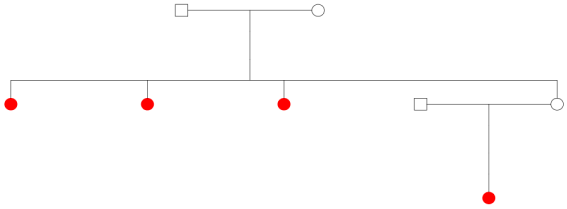

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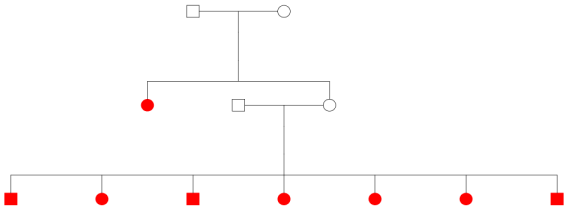

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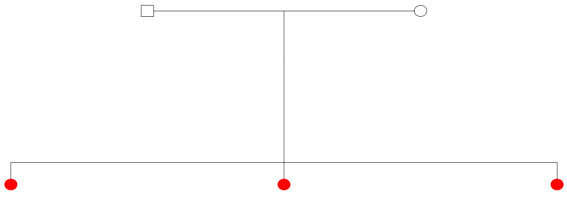

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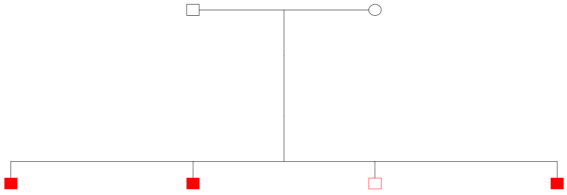

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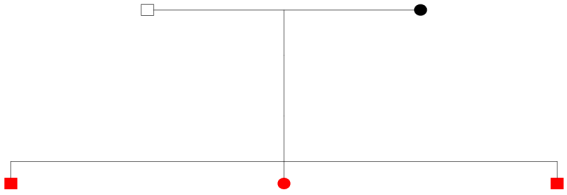

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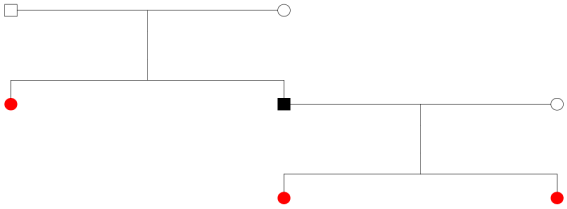

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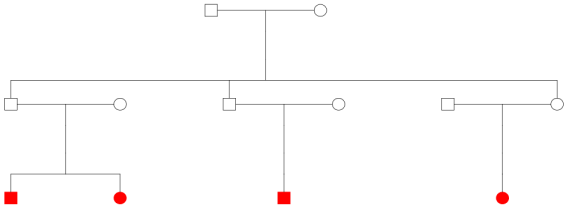

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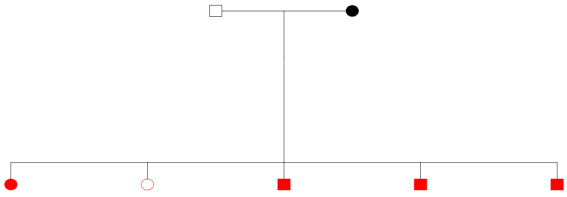

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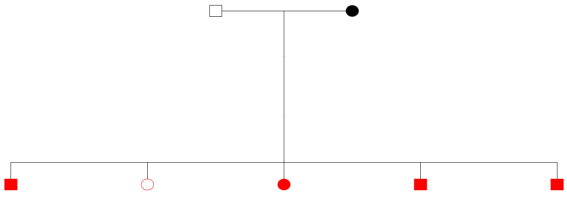

Family CU0052F

Family CU0053F

Family CU0055F

Family CU0057F

Family CU0058F

Family CU0059F

Family CU0060F

Family CU0064F

Family CU0065F

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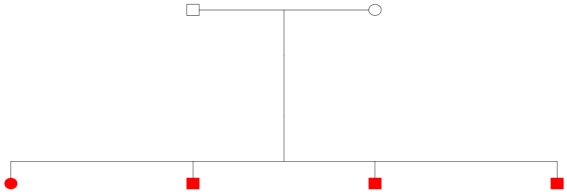
Family CU0068F

Family CU0070F

Family CU0071F



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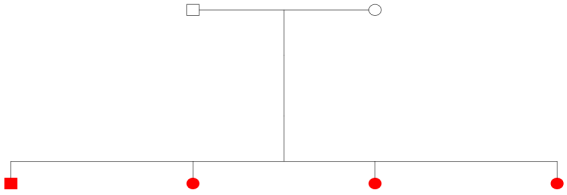

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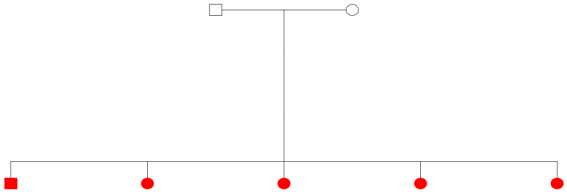

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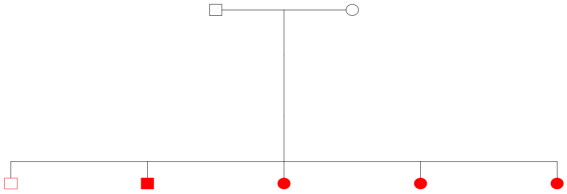
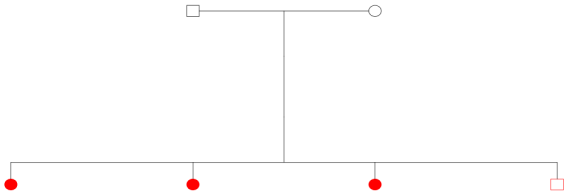
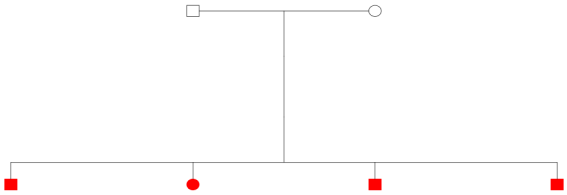


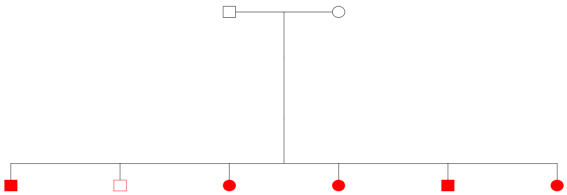
Family CU0078F



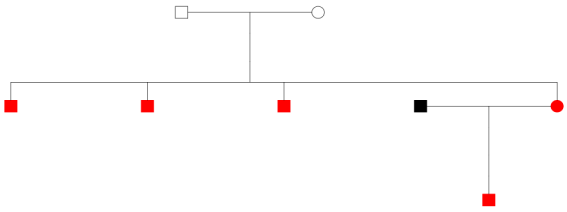
Family CU0079F



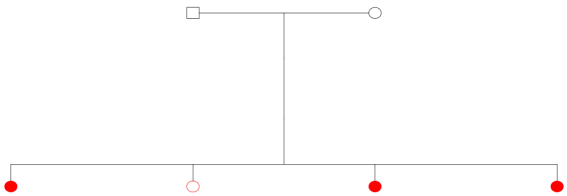
Family CU0081F



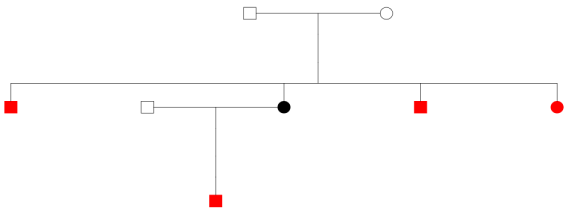
Family CU0082F



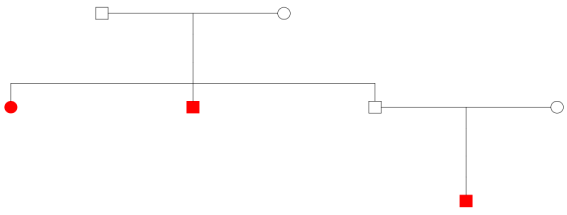
Family CU0083F



Family CU0032F



Family CU0042F



Family CU0051F

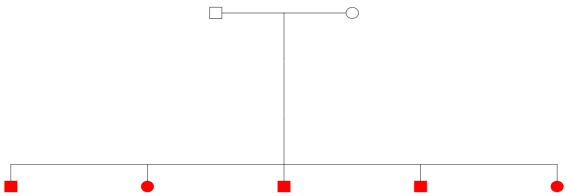


Figure S3. QQ plots for CHP-NPL$_{Pairs}$ under the null hypothesis of no linkage

One-thousand replicates of exomes were generated under the null hypothesis of no linkage for 2,000 affected sib-pairs without missing genotype date (panel A); 2,000 affected sib-pairs with founders missing all exome data (panel B); 300 nuclear families with three affected siblings without missing genotype data (panel C); 300 nuclear families with three affected siblings with founders missing all exome data (panel D); 100 extended families without missing genotype data (panel E); and 100 extended families with founders missing all exome data (panel F); and analyzed using CHP-NPL$_{Pairs}$ obtaining analytical p-values.

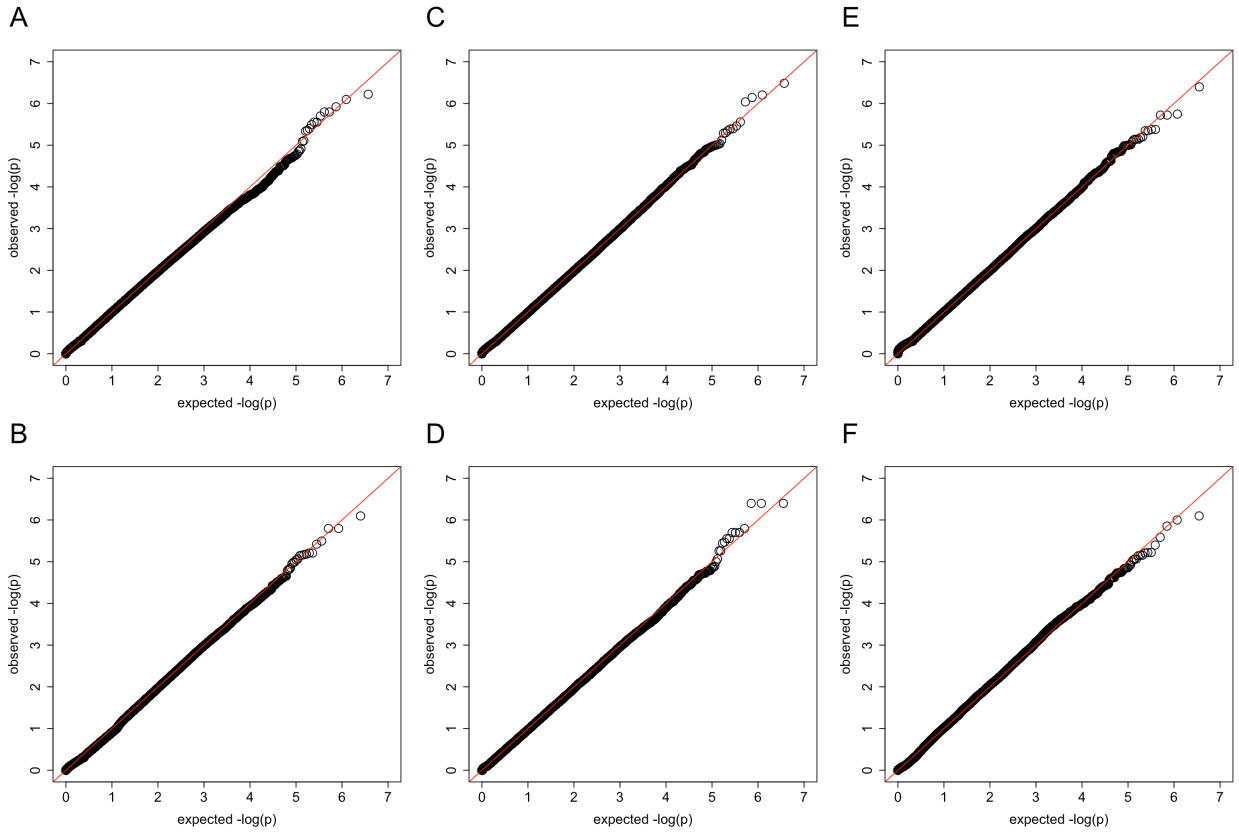


Figure S4. QQ plots for CHP-NPL$_{All}$ under the null hypothesis of no linkage

One-thousand replicates of exomes were generated under the null hypothesis of no linkage for 2,000 affected sib-pairs without missing genotype date (panel A); 2,000 affected sib-pairs with founders missing all exome data (panel B); 300 nuclear families with three affected siblings without missing genotype data (panel C); 300 nuclear families with three affected siblings with founders missing all exome data (panel D); 100 extended families without missing genotype data (panel E); and 100 extended families with founders missing all exome data (panel F); and analyzed using CHP-NPL$_{All}$ obtaining analytical p-values.

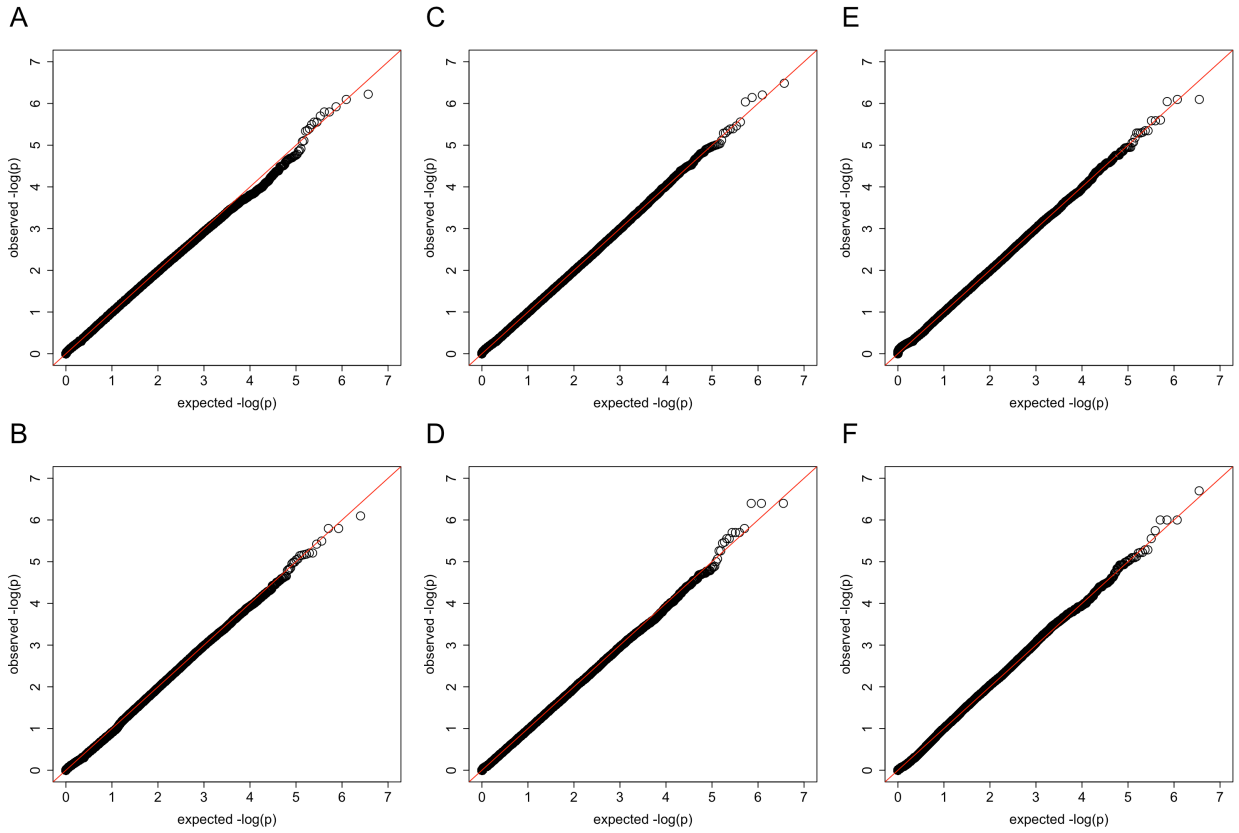


Figure S5. QQ plots for RV-NPL$_{Pairs}$ under the null hypothesis of no linkage

One-thousand replicates of exomes were generated under the null hypothesis of no linkage for 2,000 affected sib-pairs without missing genotype date (panel A); 2,000 affected sib-pairs with founders missing all exome data (panel B); 300 nuclear families with three affected siblings without missing genotype data (panel C); 300 nuclear families with three affected siblings with founders missing all exome data (panel D); 100 extended families without missing genotype data (panel E); and 100 extended families with founders missing all exome data (panel F); and analyzed using RV-NPL$_{Pairs}$ obtaining empirical p-values using 1,000,000 permutations. The observed plateau is due to the number of permutations performed.

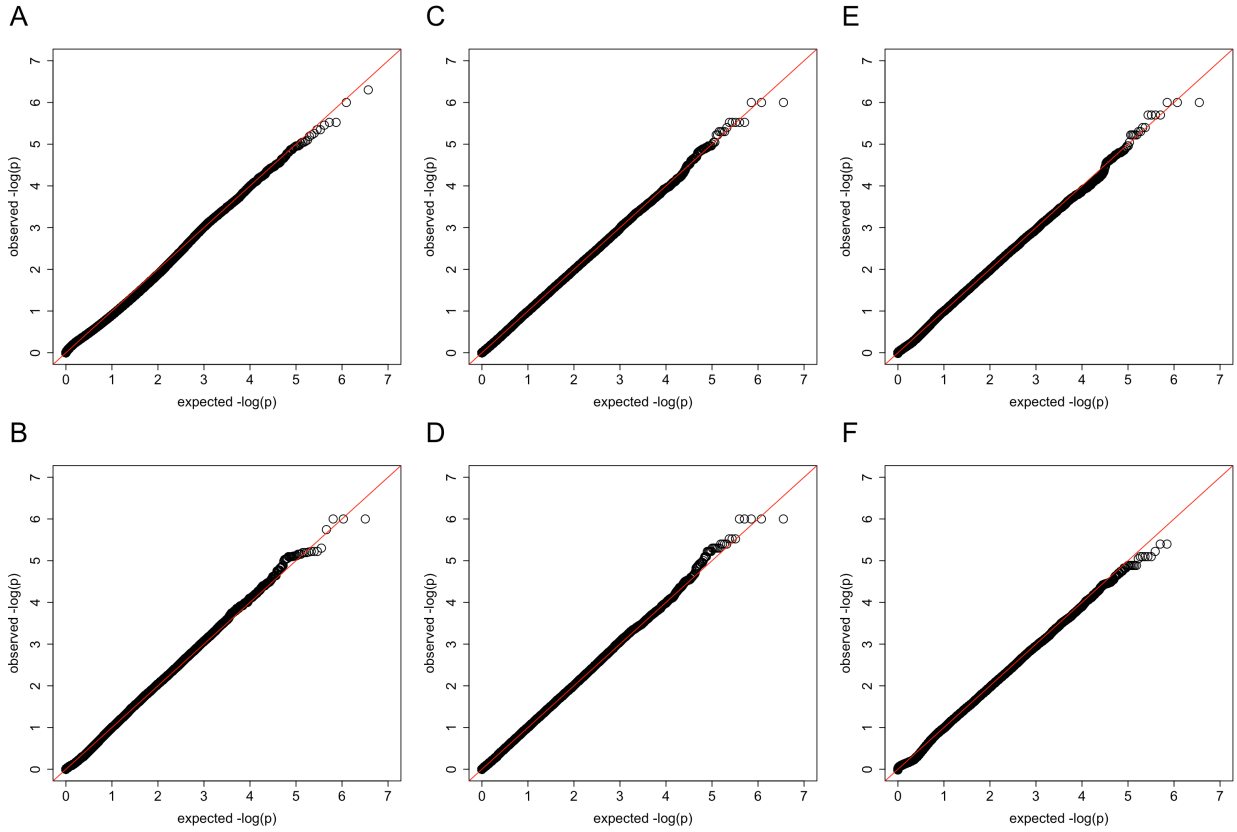


Figure S6. QQ plots for RV-NPL$_{All}$ under the null hypothesis of no linkage

One-thousand replicates of exomes were generated under the null hypothesis of no linkage for 2,000 affected sib-pairs without missing genotype date (panel A); 2,000 affected sib-pairs with founders missing all exome data (panel B); 300 nuclear families with three affected siblings without missing genotype data (panel C); 300 nuclear families with three affected siblings with founders missing all exome data (panel D); 100 extended families without missing genotype data (panel E); and 100 extended families with founders missing all exome data (panel F); and analyzed using RV-NPL$_{All}$ obtaining empirical p-values using 1,000,000 permutations. The observed plateau is due to the number of permutations performed.

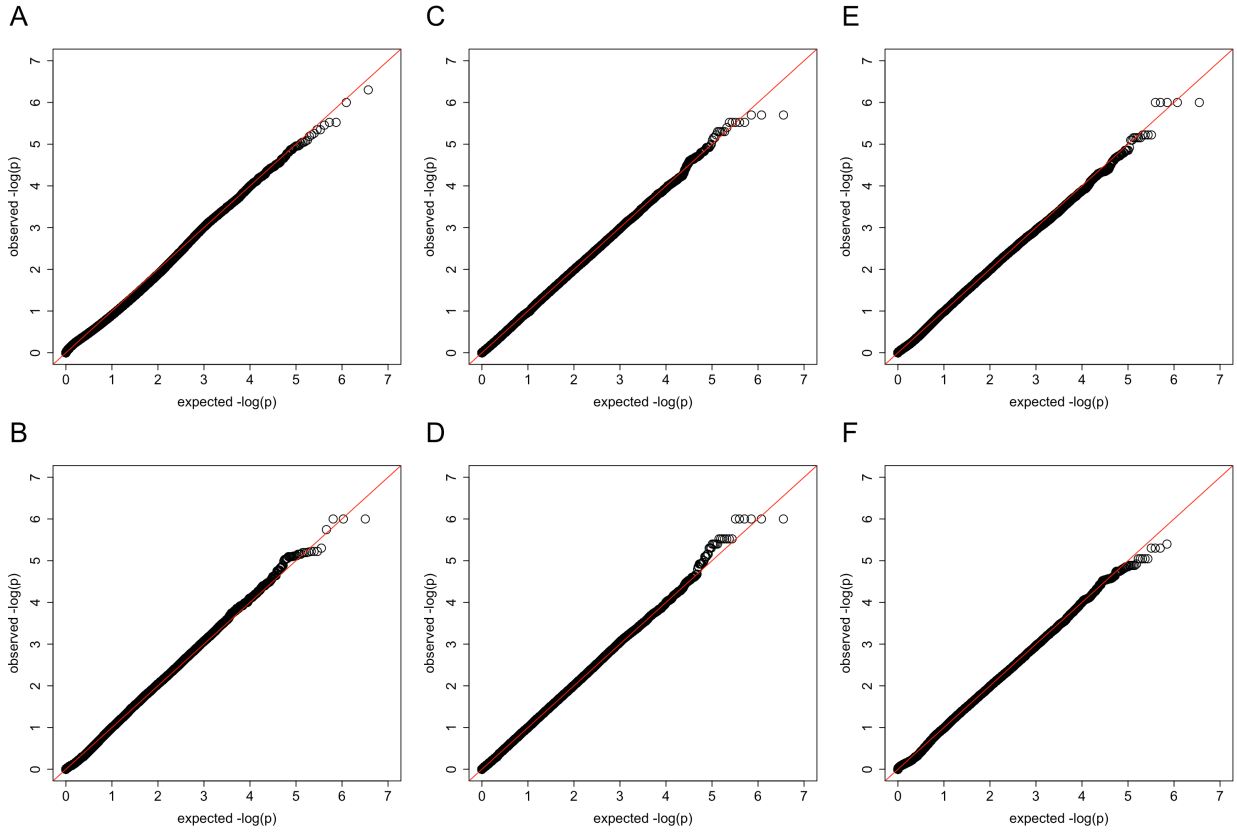
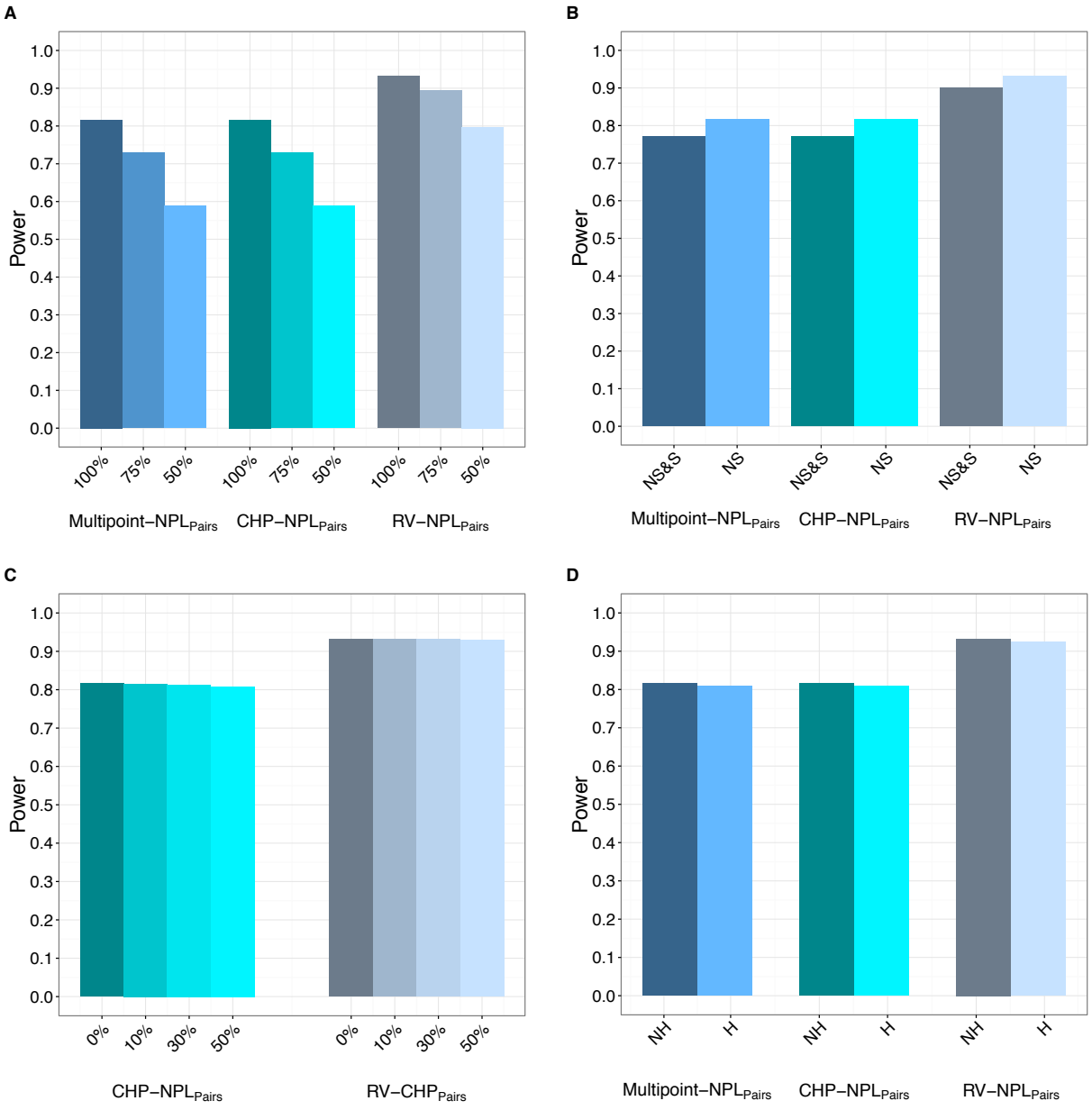


Figure S7. Power comparison for NPL_{Pairs} for nuclear families with three affected siblings

Genotypes were generated for 300 nuclear families with three affected siblings conditional on affection status assuming a multiplicative model in which each causal variant within a gene region has an OR of 5.0. Analysis was performed using RV-NPL_{Pairs}, CHP-NPL_{Pairs}, and Multipoint-NPL_{Pairs}: with 100%, 75% and 50% of the variant being causal and the remaining non-causal (OR=1.0) (panel A); with only causal nonsynonymous (NS) variants as well as with causal nonsynonymous (NS) and non-causal synonymous (S) variants (panel B); with 0%, 10%, 30%, and 50% of the founders missing all genotype data (panel C); and with no heterogeneity (NH), i.e. 300 linked families as well as with locus heterogeneity (H), i.e., 300 linked and 150 unlinked families (panel D).


A
Power
1.0
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75%
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100%
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50%
Multipoint–NPL$_{Pairs}$
CHP–NPL$_{Pairs}$
RV–NPL$_{Pairs}$
B
Power
NS&S
NS
NS&S
NS
NS&S
NS
Multipoint–NPL$_{Pairs}$
CHP–NPL$_{Pairs}$
RV–NPL$_{Pairs}$
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Power
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50%
0%
10%
30%
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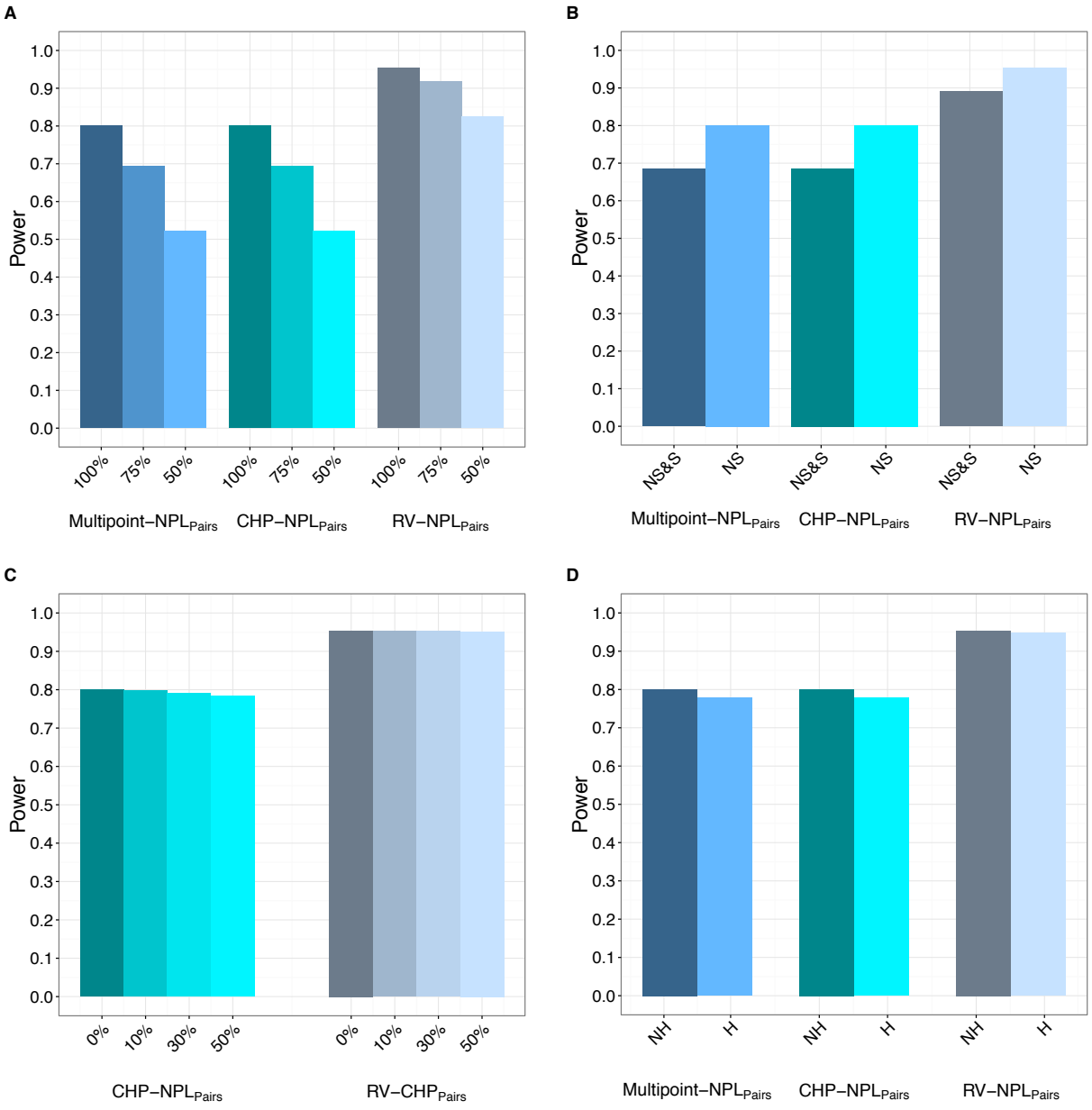
CHP–NPL$_{Pairs}$
RV–CHP$_{Pairs}$
D
Power
NH
H
NH
H
NH
H
Multipoint–NPL$_{Pairs}$
CHP–NPL$_{Pairs}$
RV–NPL$_{Pairs}$

Figure S8. Power comparison for NPL_{Pairs} on affected sibpairs

Genotypes were generated for 2,000 nuclear families with affected sibpairs conditional on affection status assuming a multiplicative model in which each causal variant within a gene region has an OR of 5.0. Analysis was performed using RV-NPL_{Pairs}, CHP-NPL_{Pairs}, and Multipoint-NPL_{Pairs}: with 100%, 75% and 50% of the variant being causal and the remaining non-causal (OR=1.0) (panel A); with only causal nonsynonymous (NS) variants as well as with causal nonsynonymous (NS) and non-causal synonymous (S) variants (panel B); with 0%, 10%, 30%, and 50% of the founders missing all genotype data (panel C); and with no heterogeneity (NH), i.e. 2,000 linked families as well as with locus heterogeneity (H), i.e., 2,000 linked and 1,000 unlinked families (panel D).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Multipoint–NPL$_{Pairs}$
CHP–NPL$_{Pairs}$
RV–NPL$_{Pairs}$
B
Power
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NS
Multipoint–NPL$_{Pairs}$
CHP–NPL$_{Pairs}$
RV–NPL$_{Pairs}$
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Power
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CHP–NPL$_{Pairs}$
RV–CHP$_{Pairs}$
D
Power
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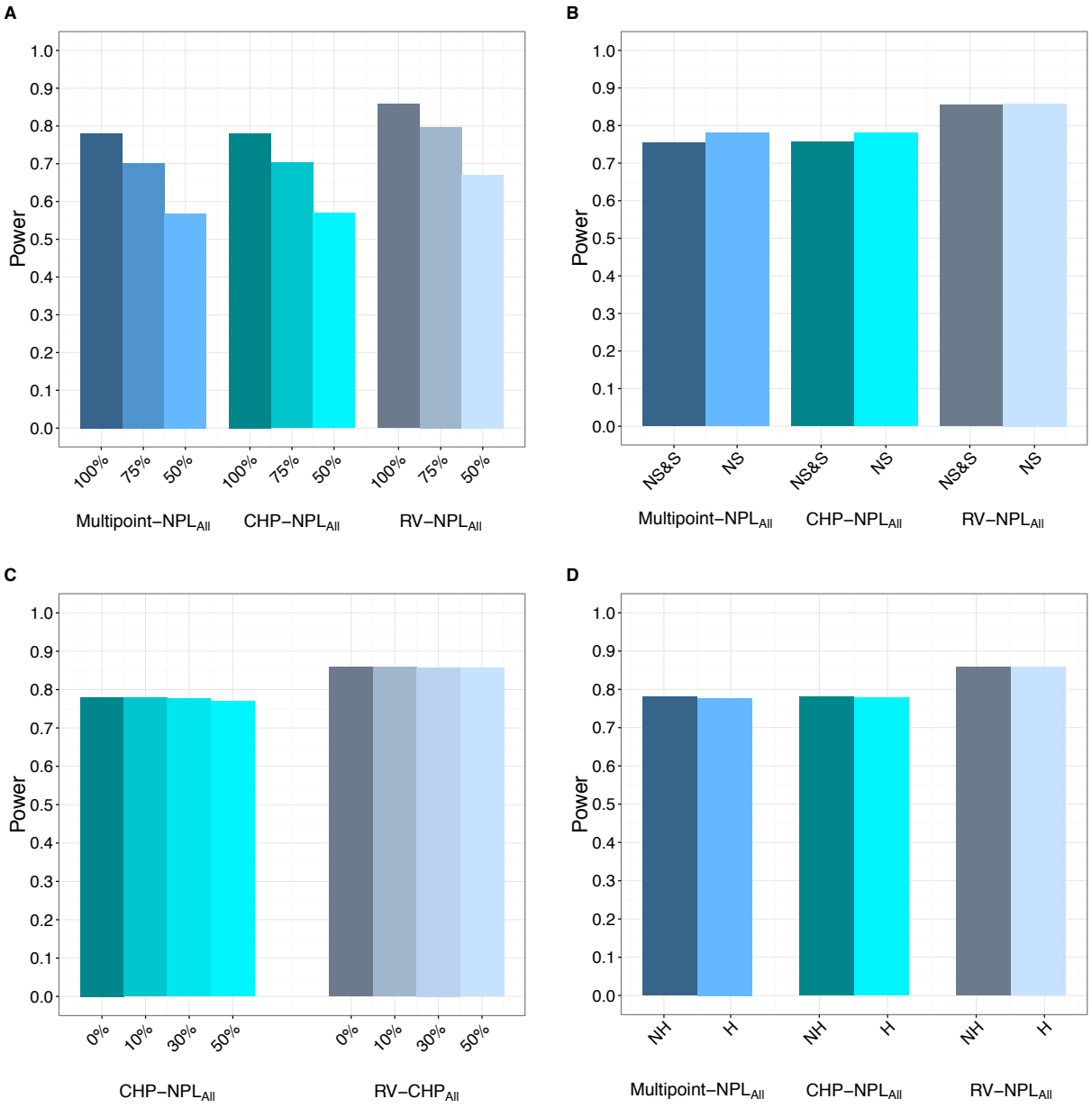
NH
H
Multipoint–NPL$_{Pairs}$
CHP–NPL$_{Pairs}$
RV–NPL$_{Pairs}$

Figure S9. Power comparison for NPL_{All} on extended families

Genotypes were generated for 100 extended families conditional on affection status assuming a multiplicative model in which each causal variant within a gene region has an OR of 5.0. Analysis was performed using RV-NPL_{All}, CHP-NPL_{All}, and Multipoint-NPL_{All}: with 100%, 75% and 50% of the variant being causal and the remaining non-causal (OR=1.0) (panel A); with only causal nonsynonymous (NS) variants as well as with causal nonsynonymous (NS) and non-causal synonymous (S) variants (panel B); with 0%, 10%, 30%, and 50% of the founders missing all genotype data (panel C); and with no heterogeneity (NH), i.e. 100 linked families as well as with locus heterogeneity (H), i.e., 100 linked and 50 unlinked families (panel D).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Multipoint–NPL$_{All}$
CHP–NPL$_{All}$
RV–NPL$_{All}$
B
Power
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NS&S
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NS&S
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Multipoint–NPL$_{All}$
CHP–NPL$_{All}$
RV–NPL$_{All}$
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CHP–NPL$_{All}$
RV–CHP$_{All}$
D
Power
NH
H
NH
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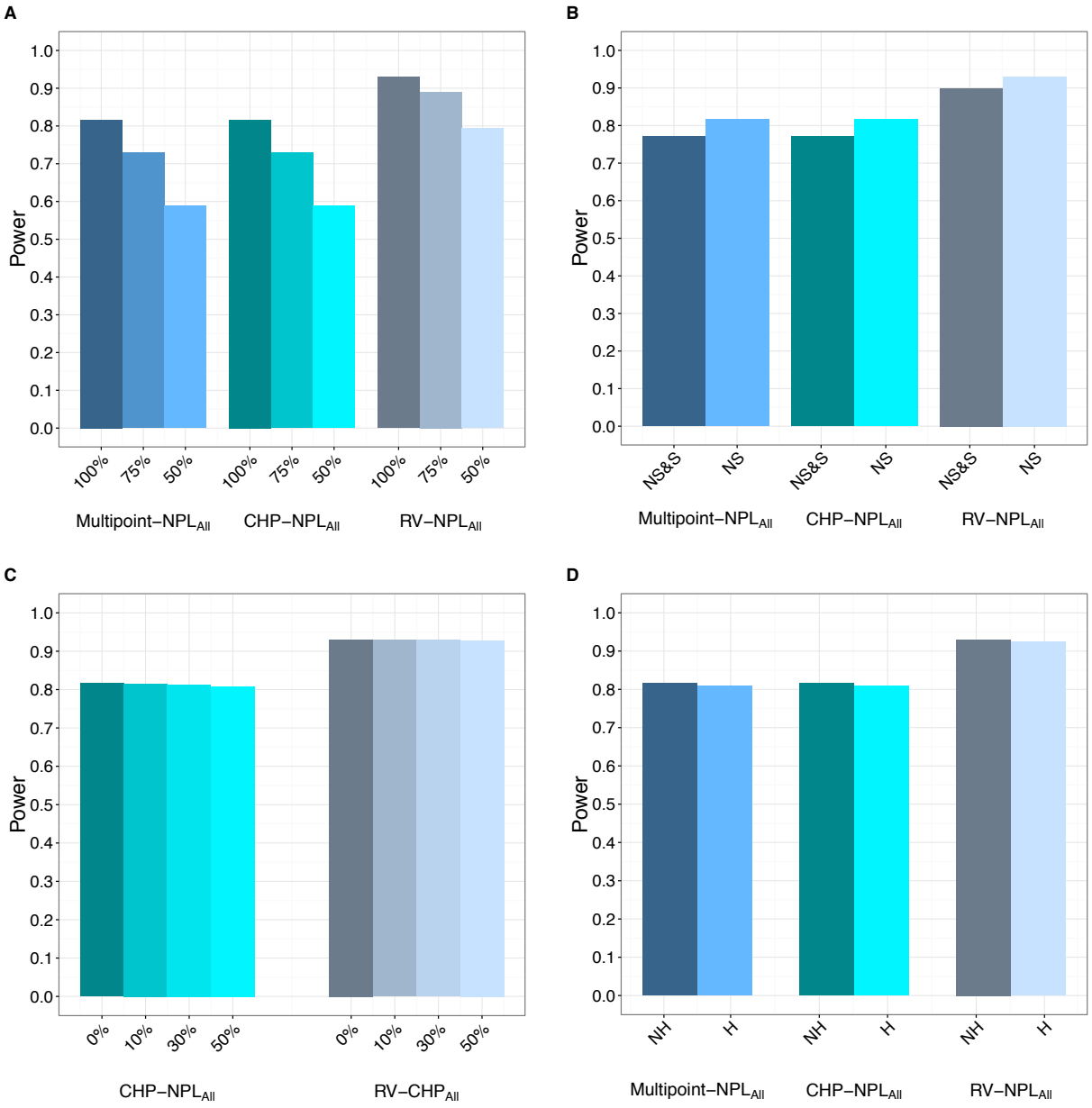
NH
H
Multipoint–NPL$_{All}$
CHP–NPL$_{All}$
RV–NPL$_{All}$

Figure S10. Power comparison for NPL_{All} on nuclear families with three affected siblings

Genotypes were generated for 300 nuclear families with three affected siblings conditional on affection status assuming a multiplicative model in which each causal variant within a gene region has an OR of 5.0. Analysis was performed using RV-NPL_{All}, CHP-NPL_{All}, and Multipoint-NPL_{All}: with 100%, 75% and 50% of the variant being causal and the remaining non-causal (OR=1.0) (panel A); with only causal nonsynonymous (NS) variants as well as with causal nonsynonymous (NS) and non-causal synonymous (S) variants (panel B); with 0%, 10%, 30%, and 50% of the founders missing all genotype data (panel C); and with no heterogeneity (NH), i.e. 100 linked families as well as with locus heterogeneity (H), i.e., 300 linked and 150 unlinked families (panel D).


A
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Multipoint–NPL$_{All}$
CHP–NPL$_{All}$
RV–NPL$_{All}$
B
Power
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Multipoint–NPL$_{All}$
CHP–NPL$_{All}$
RV–NPL$_{All}$
C
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CHP–NPL$_{All}$
RV–CHP$_{All}$
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H
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NH
H
Multipoint–NPL$_{All}$
CHP–NPL$_{All}$
RV–NPL$_{All}$

Table S1: The Ethnicities of Alzheimer's disease families included in the analysis

Ethnicity	Number of Families	Family IDs
Dominican	62	CU0002F, CU0003F[a], CU0004F[^], CU0005F[a], CU0006F[*a], CU0007F, CU0008F, CU0009F[c], CU0010F, CU0012F, CU0013F[a], CU0014F, CU0015F, CU0016F[a], CU0017F[^], CU0018F, CU0019F[^a], CU0020F, CU0022F, CU0023F[*], CU0024F, CU0025F, CU0026F, CU0029F, CU0030F[*a], CU0033F, CU0035F[^], CU0036F, CU0037F, CU0038F[*], CU0039F[a], CU0040F[a], CU0041F[a], CU0043F[c], CU0044F[a], CU0045F[c], CU0046F, CU0047F, CU0048F[^], CU0049F[*], CU0050F, CU0052F, CU0053F, CU0055F[^], CU0057F, CU0058F, CU0059F, CU0060F[a], CU0064F[a], CU0065F, CU0067F[*a], CU0068F[^], CU0070F[^a], CU0071F[a], CU0073F[^a], CU0075F[^], CU0076F[*], CU0078F[a], CU0079F[^], CU0081F[a], CU0082F, CU0083F[a]
European Descent	41	LD0168F, LD0179F, LD0223F, LD0232F, LD0241F[d], LD0254F, LD0307F, LD0856F, LD0949F, LD1012F[d], LD1223F, LD1260F, LD1265F, LD1315F[b], LD1329F[*], LD1579F[d], NC0049F, NC0131F, NC0205F[^], NC0302F, UM0002F, UM0146F[^b], UM0147F[d], UM0152F, UM0170F, UM0196F[d], UM0304F, UM0453F, UM0458F, UM0460F, UM0463F[^b], UM0464F, UP0001F, UP0002F, UP0003F, UP0004F[d], UP0005F, UP0006F, UP0007F, UP0008F, VU0072F
Puerto Rican	3	CU0032F, CU0042F, CU0051F
Dutch Isolate	1	203[d]

[^]Pedigrees with excess RV sharing for gene *PSMF1*.
*Pedigrees with excess RV sharing for gene *PTPN21*.
[a]Pedigrees with excess RV sharing for gene *ABCA7*; [b]Pedigrees with excess RV sharing for gene *ACE*;
[c]Pedigrees with excess RV sharing for gene *EPHA1*; [d]Pedigrees with excess RV sharing for gene *SORL1*.

Table S2. Type I error rate of CHP-NPL and RV-NPL at α-level of 0.05 and 0.005

		Nuclear pedigree with two affected siblings			Nuclear pedigree with three affected siblings			Extended pedigree		
	α-level	5.0×10^{-2}	5.0×10^{-3}	1.5×10^{-5}	5×10^{-2}	5.0×10^{-3}	1.5×10^{-5}	5.0×10^{-2}	5.0×10^{-3}	1.5×10^{-5}
No missing genotype	CHP-NPL_{Pairs}	4.8×10^{-2}	4.5×10^{-3}	1.0×10^{-5}	4.9×10^{-2}	4.8×10^{-3}	1.5×10^{-5}	5.0×10^{-2}	5.0×10^{-3}	1.5×10^{-5}
	CHP-NPL_{All}	4.8×10^{-2}	4.5×10^{-3}	1.0×10^{-5}	4.9×10^{-2}	4.8×10^{-3}	1.5×10^{-5}	5.0×10^{-2}	4.9×10^{-3}	1.3×10^{-5}
	RV-NPL_{Pairs}	4.6×10^{-2}	4.3×10^{-3}	1.4×10^{-5}	4.9×10^{-2}	4.8×10^{-3}	1.7×10^{-5}	4.9×10^{-2}	4.8×10^{-3}	1.7×10^{-5}
	RV-NPL_{All}	4.6×10^{-2}	4.3×10^{-3}	1.4×10^{-5}	4.9×10^{-2}	4.9×10^{-3}	1.6×10^{-5}	4.9×10^{-2}	4.9×10^{-3}	1.0×10^{-5}
All founders missing genotype	CHP-NPL_{Pairs}	4.6×10^{-2}	4.8×10^{-3}	1.4×10^{-5}	4.6×10^{-2}	4.5×10^{-3}	1.0×10^{-5}	5.1×10^{-2}	5.3×10^{-3}	1.4×10^{-5}
	CHP-NPL_{All}	4.6×10^{-2}	4.8×10^{-3}	1.4×10^{-5}	4.6×10^{-2}	4.5×10^{-3}	1.0×10^{-5}	5.1×10^{-2}	5.2×10^{-3}	1.7×10^{-5}
	RV-NPL_{Pairs}	5.1×10^{-2}	5.2×10^{-3}	1.7×10^{-5}	5.1×10^{-2}	5.2×10^{-3}	1.7×10^{-5}	4.9×10^{-2}	4.6×10^{-3}	1.5×10^{-5}
	RV-NPL_{All}	5.1×10^{-2}	5.2×10^{-3}	1.7×10^{-5}	5.1×10^{-2}	5.2×10^{-3}	1.6×10^{-5}	5.0×10^{-2}	4.8×10^{-3}	1.5×10^{-5}

Exome-wide type I error was evaluated using data generated for 1000 exomes and analyzing each gene. Three different values for α-level are shown here: $5.0\text{x}10^{-2}$, $5.0\text{x}10^{-3}$ and 1.5×10^{-5}. Type I error rate was calculated by dividing the total number of genes with a p-value equal or smaller than the α-level value by the number of genes analyzed across all 1000 generated exomes.

Table S3. Power comparison of NPL_{Pairs} and NPL_{All} in intra-familial locus heterogeneity

	RV-NPL_{Pairs}	RV-NPL_{All}	$Z_{All} > Z_{Pairs}$[a]
Without intra-familial locus heterogeneity	0.6410	0.6411	69.08%
With intra-familial locus heterogeneity	0.2997	0.2870	38.52%

Power was compared between RV-NPL_{Pairs} and RV-NPL_{All} in extended families with and without intra-familial locus heterogeneity.

[a]Proportion of total genes that have Z-scores of RV-NPL_{All} higher than that of RV-NPL_{Pairs}

Table S4: Bioinformatic evaluation and frequencies of analyzed rare variants within *PSMF1*

dbSNP rsID	rs751905514*^	rs35236223*^	rs148476395*	rs146300768^	rs146612629	rs79465651*	rs148156083*^	rs758812434*
hg19 position	20:1106192	20:1106214	20:1115798	20:1115864	20:1115870	20:1143797	20:1145081	20:1145111
Reference Allele	A	G	A	C	T	T	G	G
Alternate Allele	G	A	G	T	A	C	A	A
cDNA change	c.181A>G	c.203G>A	c.400A>G	c.466C>T	c.472T>A	c.575T>C	c.725G>A	c.755G>A
ACC	p.Asn61Asp	p.Arg68Gln	p.Ile134Val	p.Arg156Trp	p.Phe158Ile	p.Val192Ala	p.Arg242His	p.Ser252Asn
MAF[a]	$7.22x10^{-6}$	$3.61x10^{-5}$	$6.90x10^{-5}$	$4.08x10^{-4}$	$2.78x10^{-4}$	$5.61x10^{-3}$	$1.49x10^{-3}$	$3.66x10^{-5}$
MAF (NFE)[b]	$1.58x10^{-5}$	$3.16x10^{-5}$	$1.07x10^{-4}$	$5.53x10^{-5}$	$3.95x10^{-4}$	$7.26x10^{-4}$	$2.50x10^{-3}$	0
MAF (AMR)[c]	0	$2.91x10^{-5}$	$5.96x10^{-5}$	$3.20x10^{-4}$	$5.23x10^{-4}$	$3.31x10^{-3}$	$9.30x10^{-4}$	0
GERP score	4.93	4.93	4.12	2.07	5.03	5.26	5.11	4.12
PhyloP score	3.37	6.37	2.02	0.27	0.81	4.56	8.44	3.37
CADD score[d]	18.7	34.0	6.0	23.9	22.6	12.7	28.4	12.1
FATHMM	tolerated	tolerated	tolerated	tolerated	tolerated	tolerated	tolerated	tolerated
MutationTaster	disease causing	disease causing	disease causing	polymorphism	disease causing	polymorphism	disease causing	polymorphism
Polyphen-2 HVAR	possibly damaging	probably damaging	benign	probably damaging	benign	benign	benign	benign
PROVEAN	neutral	deleterious	neutral	deleterious	neutral	neutral	deleterious	neutral
SIFT	tolerated	damaging	tolerated	damaging	tolerated	tolerated	tolerated	tolerated
LRT	deleterious	deleterious	deleterious	neutral	neutral	neutral	deleterious	deleterious

Abbreviations: ACC, amino acid change; MAF, minor allele frequency; NFE, Non-Finnish European; AMR, Latino; CADD, Combined Annotation Dependent Depletion; FATHMM, Functional Analysis through Hidden Markov Models; PROVEAN, Protein Variation Effect Analyzer; SIFT, Sorting Intolerant From Tolerant.

[a]MAFs are from gnomAD (Genome Aggregation Database) combining all populations; [b]MAFs are from gnomAD NFE population; [c]MAFs are from gnomAD AMR population; [d]Scaled CADD score.

*Variant is deemed as conserved nucleotide (both GERP and PhyloP scores > 1).

^Variant is deemed damaging by at least four of seven bioinformatics tools (variant with CADD scaled C-score >15 is deemed to be deleterious).

Table S5: Bioinformatic evaluation and frequencies of analyzed rare variants within *PTPN21*

dbSNP rsID	rs141951135*^	rs150736820*^	rs143571855	rs3825676*^	rs149927113	rs138752198*	rs146847601*^
hg19 position	14:88935348	14:88935351	14:88945312	14:88945407	14:88945485	14:88974290	14:89016641
Reference Allele	G	G	G	C	C	T	C
Alternate Allele	A	A	C	G	G	C	A
cDNA change	c.3308C>T	c.3305C>T	c.2463C>G	c.2368G>C	c.2290G>C	c.425A>G	c.121G>T
ACC	p.Pro1103Leu	p.Pro1102Leu	p.Asp821Glu	p.Gly790Arg	p.Val764Leu	p.Gln142Arg	p.Val41Leu
MAF[a]	$5.41x10^{-5}$	$1.61x10^{-3}$	$1.95x10^{-3}$	$1.84x10^{-2}$	$2.17x10^{-4}$	$3.58x10^{-4}$	$4.94x10^{-4}$
MAF (NFE)[b]	$3.58x10^{-5}$	$2.73x10^{-3}$	$1.85x10^{-5}$	$1.95x10^{-2}$	0	$6.00x10^{-4}$	$7.90x10^{-6}$
MAF (AMR)[c]	$2.08x10^{-4}$	$1.16x10^{-4}$	$7.87x10^{-4}$	$3.86x10^{-3}$	$3.74x10^{-5}$	$2.06x10^{-4}$	$1.16x10^{-4}$
GERP score	5.90	5.90	-6.17	4.66	-2.01	5.36	5.50
PhyloP score	9.48	3.71	-1.29	5.10	0.88	2.42	7.60
CADD score[d]	34.0	22.9	0.04	19.8	0.1	7.9	23.6
FATHMM	tolerated	tolerated	tolerated	tolerated	tolerated	tolerated	tolerated
MutationTaster	disease_causing	disease causing	polymorphism	disease causing	polymorphism	disease causing	disease_causing
Polyphen-2 HVAR	probably damaging	benign	benign	probably damaging	benign	benign	probably damaging
PROVEAN	deleterious	deleterious	neutral	neutral	neutral	neutral	neutral
SIFT	damaging	damaging	tolerated	damaging	tolerated	tolerated	tolerated
LRT	deleterious	deleterious	deleterious	deleterious	neutral	neutral	deleterious

Abbreviations: ACC, amino acid change; MAF, minor allele frequency; NFE, Non-Finnish European; AMR, Latino; CADD, Combined Annotation Dependent Depletion; FATHMM, Functional Analysis through Hidden Markov Models; PROVEAN, Protein Variation Effect Analyzer; SIFT, Sorting Intolerant From Tolerant.

[a]MAFs are from gnomAD (Genome Aggregation Database) combining all populations; [b]MAFs are from gnomAD NFE population; [c]MAFs are from gnomAD AMR population; [d]Scaled CADD score.

*Variant is deemed as conserved nucleotide (both GERP and PhyloP scores > 1).

^Variant is deemed damaging by at least four of seven bioinformatics tools (variant with CADD scaled C-score >15 is deemed to be deleterious).

Table S6: Bioinformatic evaluation and frequencies of analyzed rare variants within *ABCA7*

dbSNP rsID	rs146597357	rs151054304	NA*^	rs138055574	rs76282929^	rs149949633*^	rs111940546*
hg19 position	19:1041922	19:1042353	19:1043175	19:1044672	19:1048898	19:1048950	19:1051209
Reference Allele	C	C	A	G	G	G	G
Alternate Allele	A	T	G	A	C	A	T
cDNA change	c.253C>A	c.455C>T	c.715A>G	c.1144G>A	c.2274G>C	c.2326G>A	c.2740G>T
ACC	p.Leu85Met	p.Pro152Leu	p.Asn239Asp	p.Gly382Ser	p.Gln758His	p.Gly776Arg	p.Ala914Ser
MAF[a]	$3.08x10^{-4}$	$1.42x10^{-3}$	.	$5.34x10^{-5}$	$4.28x10^{-3}$	$1.13x10^{-4}$	$1.86x10^{-4}$
MAF (NFE)[b]	$4.95x10^{-5}$	$2.44x10^{-5}$	.	$2.38x10^{-5}$	$6.58x10^{-5}$	$1.95x10^{-4}$	0
MAF (AMR)[c]	$2.41x10^{-4}$	$7.63x10^{-4}$	.	0	$1.59x10^{-3}$	$8.91x10^{-5}$	$1.75x10^{-4}$
GERP score	1.68	2.06	3.04	2.83	3.99	3.99	3.4
PhyloP score	0.83	-0.85	2.17	0.73	-5.34	6.44	1.39
CADD score[d]	13.4	7.4	20.4	8.8	25.3	28.6	8.16
FATHMM	damaging	damaging	damaging	damaging	damaging	tolerated	tolerated
MutationTaster	polymorphism	polymorphism	polymorphism	polymorphism	polymorphism	disease_causing	polymorphism
Polyphen-2 HVAR	benign	benign	probably damaging	benign	probably damaging	probably damaging	benign
PROVEAN	neutral	neutral	deleterious	neutral	deleterious	deleterious	neutral
SIFT	tolerated	tolerated	damaging	tolerated	damaging	damaging	tolerated
LRT	.	.	.	.	.	.	.

Abbreviations: ACC, amino acid change; MAF, minor allele frequency; NFE, Non-Finnish European; AMR, Latino; CADD, Combined Annotation Dependent Depletion; FATHMM, Functional Analysis through Hidden Markov Models; PROVEAN, Protein Variation Effect Analyzer; SIFT, Sorting Intolerant From Tolerant.

[a]MAFs are from gnomAD (Genome Aggregation Database) combining all populations; [b]MAFs are from gnomAD NFE population; [c]MAFs are from gnomAD AMR population; [d]Scaled CADD score.

*Variant is deemed as conserved nucleotide (both GERP and PhyloP scores > 1).

^Variant is deemed damaging by at least four of seven bioinformatics tools (variant with CADD scaled C-score >15 is deemed to be deleterious).

Table S6: Bioinformatic evaluation and frequencies of analyzed rare variants within ABCA7 (continued)

dbSNP rsID	rs947668738*	rs114614802^	rs369849959	rs184590335*^	rs73505232*^	rs114782266^
hg19 position	19:1053401	19:1054324	19:1056127	19:1057919	19:1058635	19:1059056
Reference Allele	G	G	G	C	C	G
Alternate Allele	C	A	A	T	T	A
cDNA change	c.3294G>C	c.3710G>A	c.4301G>A	c.4886C>T	c.5168C>T	c.5435G>A
ACC	p.Glu1098Asp	p.Arg1237His	p.Arg1434His	p.Ser1629Leu	p.Ser1723Leu	p.Arg1812His
MAF[a]	$6.37x10^{-5}$	$2.38x10^{-3}$	$2.52x10^{-5}$	$1.29x10^{-3}$	$1.21x10^{-2}$	$1.06x10^{-2}$
MAF (NFE)[b]	0	$2.49x10^{-5}$	$1.60x10^{-5}$	0	$1.74x10^{-4}$	$6.41x10^{-3}$
MAF (AMR)[c]	$1.19x10^{-3}$	$1.03x10^{-3}$	$8.76x10^{-5}$	$9.47x10^{-3}$	$5.01x10^{-3}$	$5.35x10^{-3}$
GERP score	1.25	3.64	-2.23	4.22	4.23	0.81
PhyloP score	2.42	0.36	-0.98	7.64	2.03	4.26
CADD score[d]	22.9	32.0	2.8	35.0	33.0	21.8
FATHMM	tolerated	damaging	damaging	damaging	damaging	damaging
MutationTaster	polymorphism	polymorphism	polymorphism	disease_causing	polymorphism	polymorphism
Polyphen-2 HVAR	benign	probably damaging	benign	benign	benign	benign
PROVEAN	neutral	deleterious	neutral	deleterious	deleterious	deleterious
SIFT	tolerated	damaging	tolerated	damaging	damaging	damaging
LRT	.	.	.	.	.	.

Abbreviations: ACC, amino acid change; MAF, minor allele frequency; NFE, Non-Finnish European; AMR, Latino; CADD, Combined Annotation Dependent Depletion; FATHMM, Functional Analysis through Hidden Markov Models; PROVEAN, Protein Variation Effect Analyzer; SIFT, Sorting Intolerant From Tolerant.

[a]MAFs are from gnomAD (Genome Aggregation Database) combining all populations; [b]MAFs are from gnomAD NFE population; [c]MAFs are from gnomAD AMR population; [d]Scaled CADD score.

*Variant is deemed as conserved nucleotide (both GERP and PhyloP scores > 1).

^Variant is deemed damaging by at least four of seven bioinformatics tools (variant with CADD scaled C-score >15 is deemed to be deleterious).

Table S7: Bioinformatic evaluation and frequencies of analyzed rare variants within *ACE*

dbSNP rsID	rs148943954*^	rs3730043*^	rs765069550
hg19 position	17:61560846	17:61568577	17:61574683
Reference Allele	C	C	C
Alternate Allele	G	T	T
cDNA change	c.1513C>G	c.2747C>T	c.3877C>T
ACC	p.Pro505Ala	p.Thr916Met	p.His1293Tyr
MAF[a]	$5.37x10^{-4}$	$4.02x10^{-3}$	$2.26x10^{-5}$
MAF (NFE)[b]	$1.24x10^{-4}$	$6.50x10^{-3}$	$4.38x10^{-5}$
MAF (AMR)[c]	$7.34x10^{-4}$	$1.55x10^{-3}$	0
GERP score	4.90	4.25	-0.28
PhyloP score	3.27	2.39	0.93
CADD score[d]	25.4	28.8	15.1
FATHMM	damaging	tolerated	tolerated
MutationTaster	disease_causing	disease_causing	polymorphism
Polyphen-2 HVAR	possibly damaging	probably damaging	benign
PROVEAN	deleterious	deleterious	neutral
SIFT	damaging	damaging	damaging
LRT	deleterious	deleterious	neutral

Abbreviations: ACC, amino acid change; MAF, minor allele frequency; NFE, Non-Finnish European; AMR, Latino; CADD, Combined Annotation Dependent Depletion; FATHMM, Functional Analysis through Hidden Markov Models; PROVEAN, Protein Variation Effect Analyzer; SIFT, Sorting Intolerant From Tolerant.

[a]MAFs are from gnomAD (Genome Aggregation Database) combining all populations; [b]MAFs are from gnomAD NFE population; [c]MAFs are from gnomAD AMR population; [d]Scaled CADD score.

*Variant is deemed as conserved nucleotide (both GERP and PhyloP scores > 1).

^Variant is deemed damaging by at least four of seven bioinformatics tools (variant with CADD scaled C-score >15 is deemed to be deleterious).

Table S8: Bioinformatic evaluation and frequencies of analyzed rare variants within *EPHA1*

dbSNP rsID	rs139482378*^	rs139711610*^
hg19 position	7:143088584	7:143091417
Reference Allele	C	C
Alternate Allele	T	T
cDNA change	c.2897G>A	c.2372G>A
ACC	Arg966His	p.Arg791His
MAF[a]	$6.01x10^{-4}$	$3.26x10^{-4}$
MAF (NFE)[b]	$1.12x10^{-3}$	$1.55x10^{-5}$
MAF (AMR)[c]	$3.67x10^{-4}$	$3.11x10^{-4}$
GERP score	5.24	4.67
PhyloP score	2.51	7.56
CADD score[d]	35.0	35.9
FATHMM	tolerated	damaging
MutationTaster	disease_causing	disease_causing
Polyphen-2 HVAR	probably damaging	probably damaging
PROVEAN	deleterious	deleterious
SIFT	damaging	damaging
LRT	deleterious	deleterious

Abbreviations: ACC, amino acid change; MAF, minor allele frequency; NFE, Non-Finnish European; AMR, Latino; CADD, Combined Annotation Dependent Depletion; FATHMM, Functional Analysis through Hidden Markov Models; PROVEAN, Protein Variation Effect Analyzer; SIFT, Sorting Intolerant From Tolerant.

[a]MAFs are from gnomAD (Genome Aggregation Database) combining all populations; [b]MAFs are from gnomAD NFE population; [c]MAFs are from gnomAD AMR population; [d]Scaled CADD score.

*Variant is deemed as conserved nucleotide (both GERP and PhyloP scores > 1).

^Variant is deemed damaging by at least four of seven bioinformatics tools (variant with CADD scaled C-score >15 is deemed to be deleterious).

Table S9: Bioinformatic evaluation and frequencies of analyzed rare variants within *SORL1*

dbSNP rsID	rs1051430452*^	rs150609294*^	rs139710266*^	rs62617129	rs62622819	rs140327834*^	rs142884576*^
hg19 position	11:121360768	11:121384931	11:121384991	11:121444958	11:121485599	11:121495816	11:121498300
Reference Allele	A	A	A	A	T	A	C
Alternate Allele	G	C	G	G	A	T	T
cDNA change	c.707A>G	c.1112A>C	c.1172A>G	c.3346A>G	c.5439T>A	c.6194A>T	c.6401C>T
ACC	p.Asp236Gly	p.Asn371Thr	p.Tyr391Cys	p.Ile1116Val	p.His1813Gln	p.Asp2065Val	p.Thr2134Met
MAF[a]	$3.98x10^{-6}$	$1.37x10^{-3}$	$3.18x10^{-5}$	$5.31x10^{-3}$	$4.99x10^{-3}$	$2.54x10^{-3}$	$3.29x10^{-4}$
MAF (NFE)[b]	$8.79x10^{-6}$	$2.17x10^{-3}$	$4.40x10^{-5}$	$8.25x10^{-3}$	$8.97x10^{-3}$	$4.10x10^{-3}$	$5.89x10^{-4}$
MAF (AMR)[c]	0	$1.41x10^{-4}$	0	$2.65x10^{-3}$	$1.89x10^{-3}$	$1.53x10^{-3}$	$5.64x10^{-5}$
GERP score	5.68	5.66	5.56	-5.57	-8.35	5.32	5.74
PhyloP score	8.73	9.24	9.24	-0.74	-1.34	8.64	2.63
CADD score[d]	33.0	24.1	25.0	0.05	9.4	25.5	23.9
FATHMM	tolerated	tolerated	tolerated	damaging	tolerated	tolerated	damaging
MutationTaster	disease_causing	disease_causing	disease_causing	polymorphism	disease_causing	disease_causing	disease_causing
Polyphen-2 HVAR	probably damaging	possibly damaging	probably damaging	benign	benign	probably damaging	benign
PROVEAN	deleterious	deleterious	deleterious	neutral	neutral	deleterious	neutral
SIFT	damaging	damaging	tolerated	tolerated	tolerated	tolerated	damaging
LRT	deleterious	deleterious	deleterious	neutral	neutral	deleterious	neutral

Abbreviations: ACC, amino acid change; MAF, minor allele frequency; NFE, Non-Finnish European; AMR, Latino; CADD, Combined Annotation Dependent Depletion; FATHMM, Functional Analysis through Hidden Markov Models; PROVEAN, Protein Variation Effect Analyzer; SIFT, Sorting Intolerant From Tolerant.

[a]MAFs are from gnomAD (Genome Aggregation Database) combining all populations; [b]MAFs are from gnomAD NFE population; [c]MAFs are from gnomAD AMR population; [d]Scaled CADD score.

*Variant is deemed as conserved nucleotide (both GERP and PhyloP scores > 1).

^Variant is deemed damaging by at least four of seven bioinformatics tools (variant with CADD scaled C-score >15 is deemed to be deleterious).

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