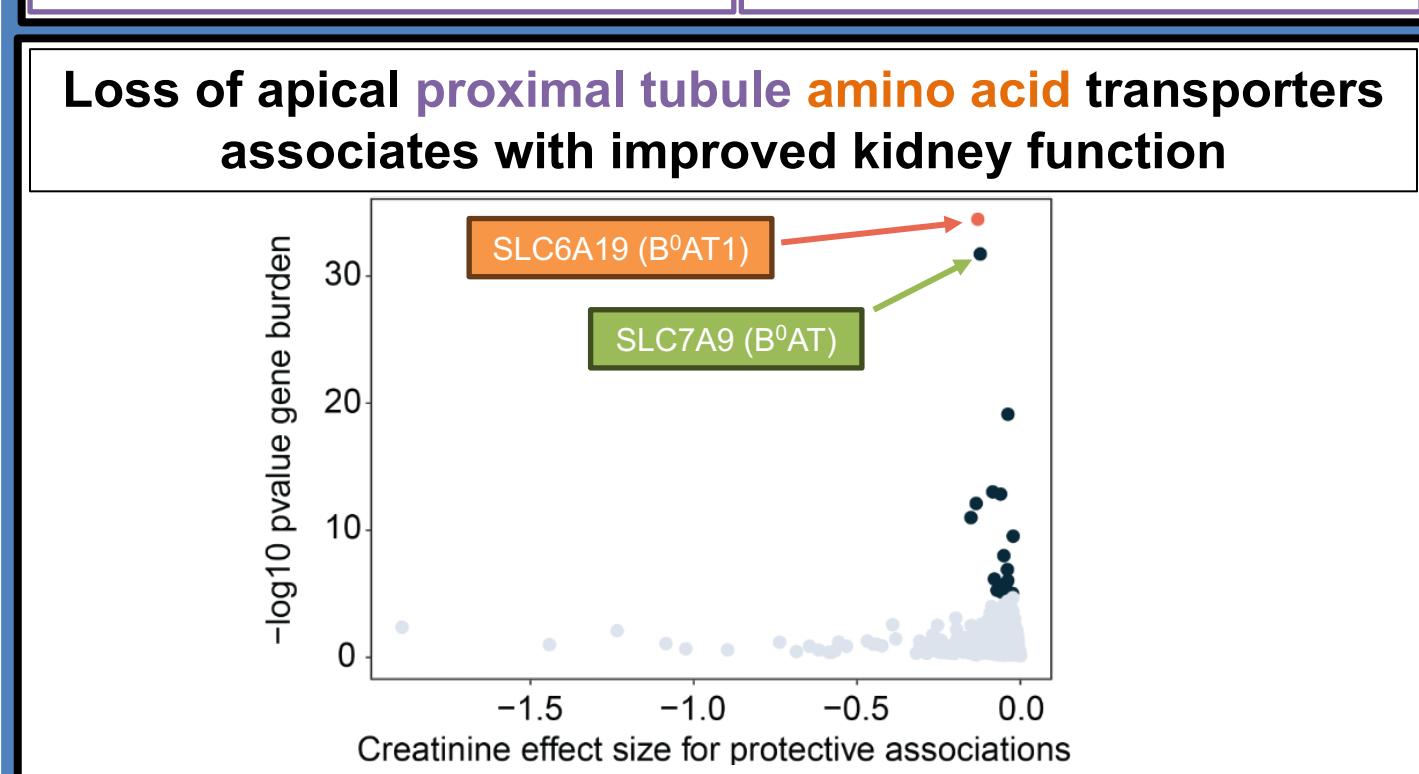
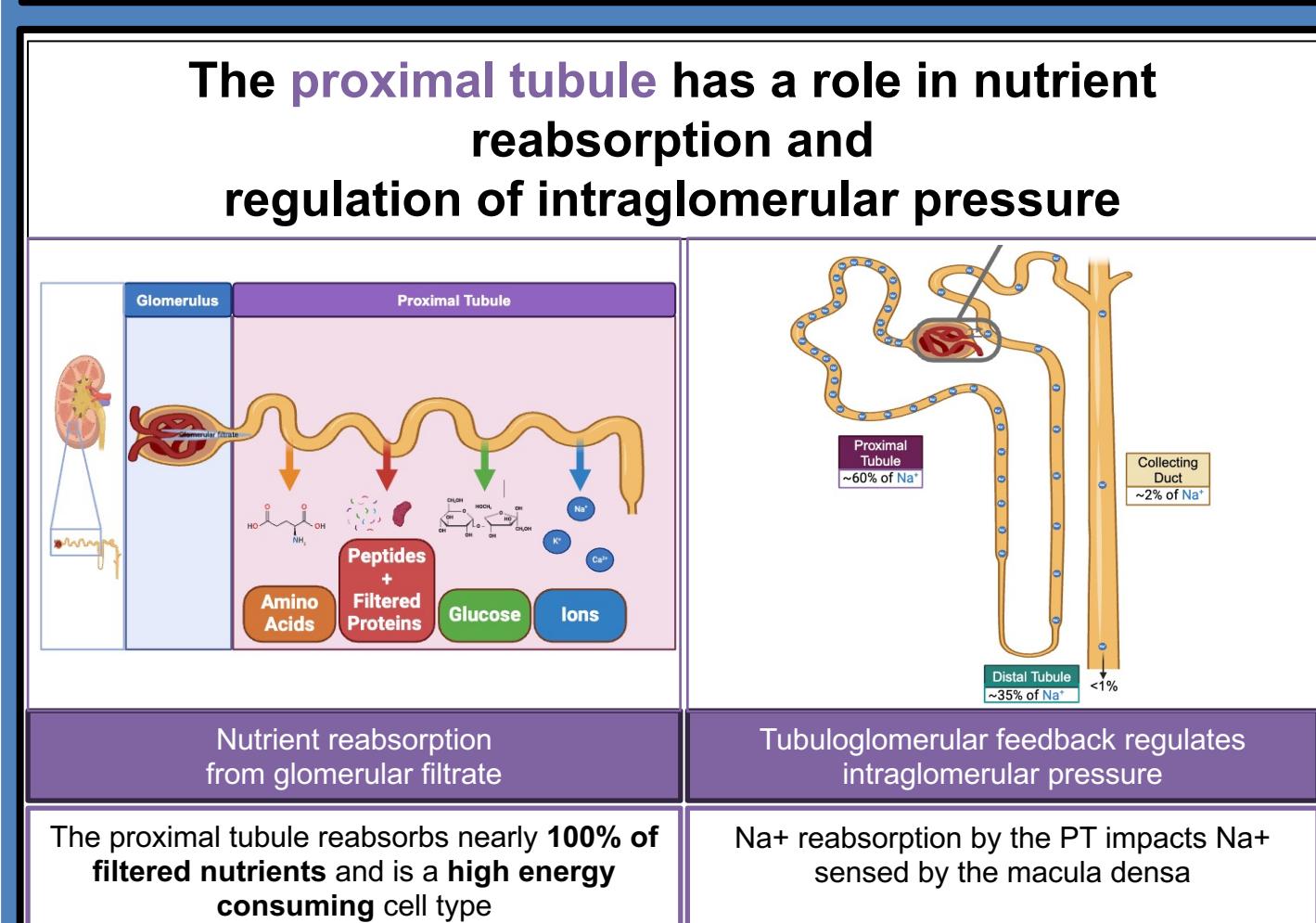
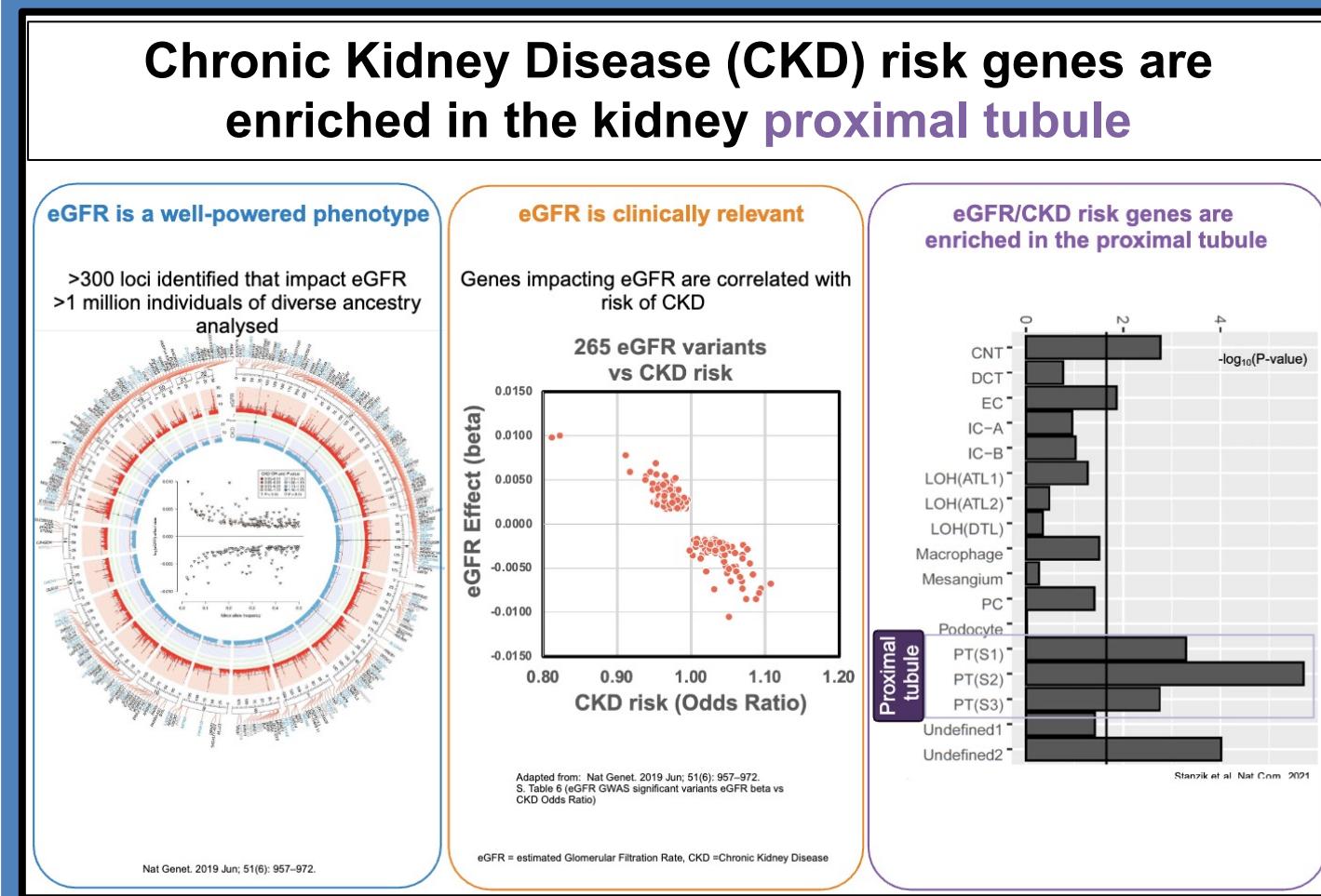


SLC6A19 (B<sup>0</sup>AT1) allelic series: loss of function is associated with improved kidney function

Sahar V. Mozaffari, Yannan Xi, Laura Sanman, Julie C. Ullman, Susan Limb, Maarten Hoek, Karol Estrada, Robert R. Graham

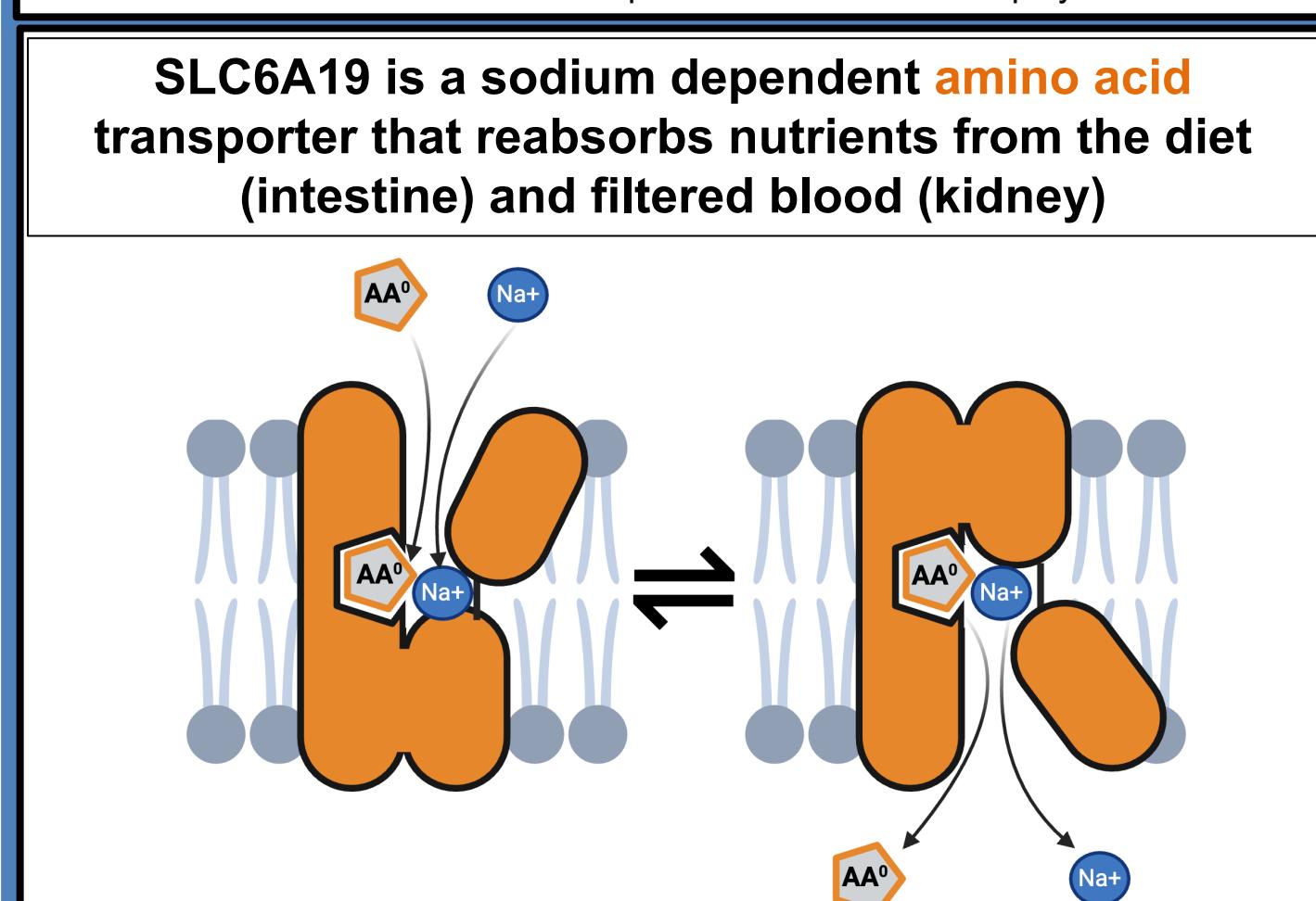
Maze Therapeutics, South San Francisco, CA

## Background

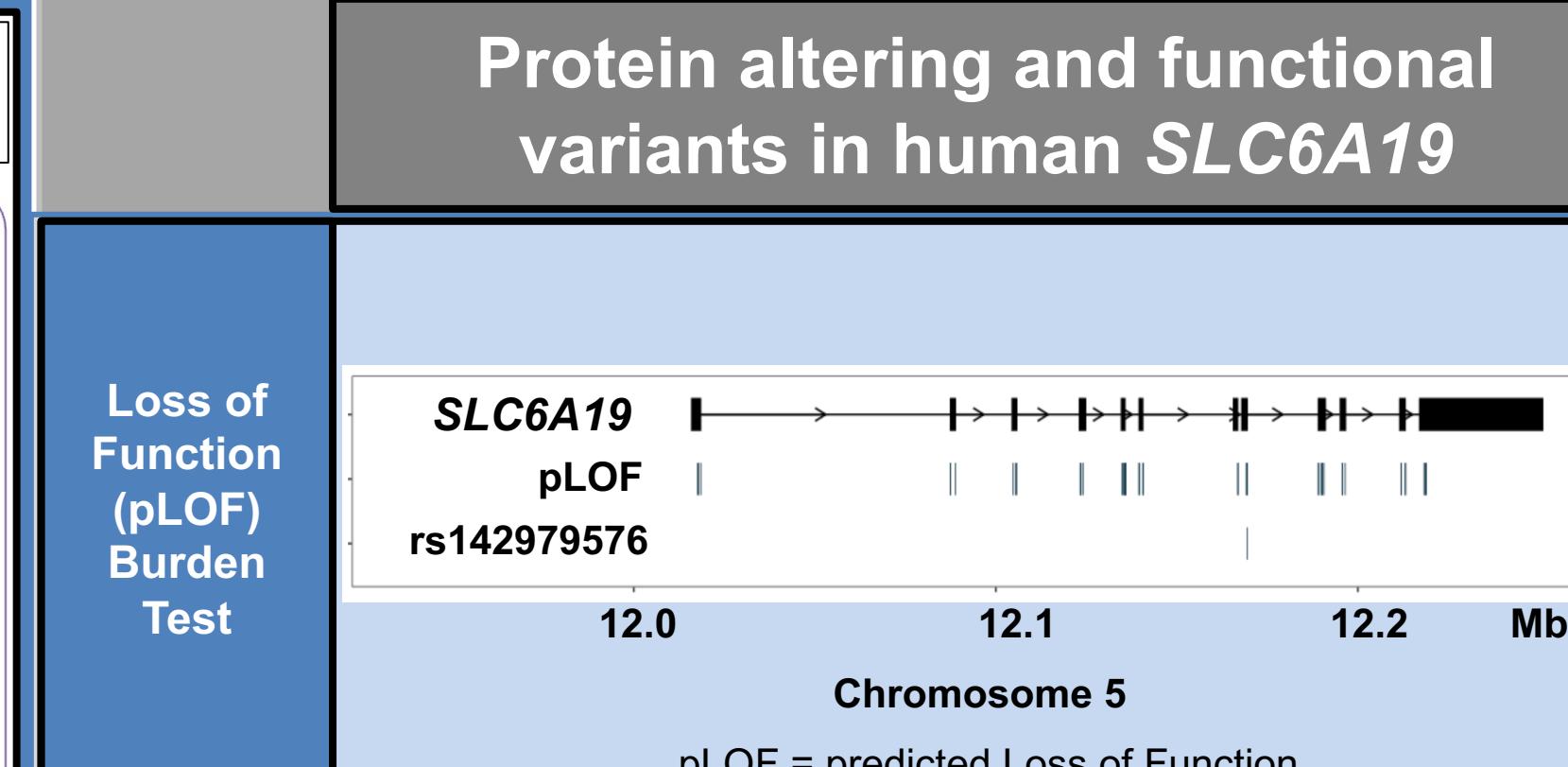


Genome-wide burden test for all pLOF and missense variants (MAF<1%) using UK Biobank<sup>1</sup> exome sequencing data (European ancestry)

Genes with P < 1 x 10<sup>-5</sup> for reduced plasma creatinine are displayed in black



## Protein altering and functional variants in human SLC6A19



## Allelic Series: Variant Definitions

pLOF = predicted Loss Of Function

Variants that prevent expression of one copy of SLC6A19  
Variants include: premature stop gain/nonsense, frameshift, essential splice site, where variants are predicted to cause non-sense mediated decay of the SLC6A19 mRNA transcript.

pLOF variants are rare and most carriers have only 1 copy of a pLOF, leading to haploinsufficiency (50% loss of gene copy number)

Rare Missense Burden Test

SLC6A19 12.0 12.1 12.2 Mbp  
Missense (MAF < 0.001)

Missense variants change one amino acid residue in the protein.

Missense variants can have:  
- little impact on function (benign)  
- moderate or nearly complete loss of function (hypomorphic)  
- altered or gain of function

Rare missense variants with a Minor Allele Frequency (MAF) < 0.001 tend to be enriched for hypomorphic variants.

Most carriers of a rare missense variant bear one copy (heterozygous). To have sufficient power to test for association, a rare missense burden test aggregates all individuals carrying a qualifying variant.

Known Hartnup Disease Missense Variants

SLC6A19 12.0 12.1 12.2 Mbp  
D173N (rs121434346)  
Hartnup Missense

Hartnup's Disease requires a person to carry 2 copies of a hypomorphic missense or loss of function SLC6A19 variant (Autosomal recessive phenotype).

Hartnup's Disease is characterized by excess amino acids in urine (aminoaciduria) and stool. Hartnup's Disease can cause skin rashes and neurological manifestations, typically the result of malnutrition. With a normal diet symptoms recede and, in fact, most individuals are unaware they are carriers.

D173N is a hypomorphic missense variant observed in Hartnup's cases. D173N is relatively common in people of Northern European ancestry (MAF=0.003). Most carriers of D173N have only 1 copy (heterozygous).

Regulatory variant (eQTL)

SLC6A19 12.0 12.1 12.2 Mbp  
eQTL (rs11133665)

An eQTL = mRNA expression Quantitative Trait Locus

Search for common variants that affect levels of SLC6A19 mRNA in the kidney tubule identified rs11133665.

The "A" allele of rs11133665 is associated with increased mRNA expression of SLC6A19 in kidney tubules. rs11133665, A has a MAF ~25% in people of European ancestry

nephQTL2 Tubule<sup>1</sup> Variant ID: rs11133665, G, A Gene symbol: SLC6A19 SNP Beta: 0.193 SNP P-Value: 5.48e-10

Protein levels

eQTL = mRNA expression Quantitative Trait Locus

<sup>1</sup> https://www.nature.com/articles/s41467-023-37691-7

<sup>2</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>3</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>4</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>5</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>6</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>7</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>8</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>9</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>10</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>11</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>12</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>13</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>14</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>15</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>16</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>17</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>18</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>19</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>20</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>21</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>22</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>23</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>24</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>25</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>26</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>27</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>28</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>29</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>30</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>31</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>32</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>33</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>34</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>35</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>36</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>37</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>38</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>39</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>40</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>41</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>42</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>43</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>44</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>45</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>46</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>47</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>48</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>49</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>50</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>51</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>52</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>53</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>54</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>55</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>56</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>57</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>58</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>59</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>60</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>61</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>62</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>63</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>64</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>65</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>66</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>67</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>68</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>69</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>70</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>71</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>72</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>73</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>74</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>75</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>76</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>77</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>78</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>79</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>80</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>81</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>82</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>83</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>84</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>85</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>86</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>87</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>88</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>89</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>90</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>91</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>92</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200000/

<sup>93</sup> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC620